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Dayton

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[54] **MINIMALLY INVASIVE BIOACTIVATED ENDOPROSTHESIS FOR VESSEL REPAIR**

[75] Inventor: **Michael P. Dayton**, 14802 Hadleigh Way, Tampa, Fla. 33624

[73] Assignees: **Michael Peck Dayton**, Tampa, Fla.; **Kenneth Granke**, Morgantown, W. Va.

[21] Appl. No.: **457,850**

[22] Filed: **Jun. 1, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 204,947, Mar. 2, 1994, Pat. No. 5,449,382, which is a continuation of Ser. No. 971,217, Nov. 4, 1992, abandoned.

[51] **Int. Cl.**[6] **A61F 2/06**

[52] **U.S. Cl.** **623/1**; 623/12; 623/901; 604/104; 604/107

[58] **Field of Search** 623/1, 12, 901; 604/95, 104, 107, 114

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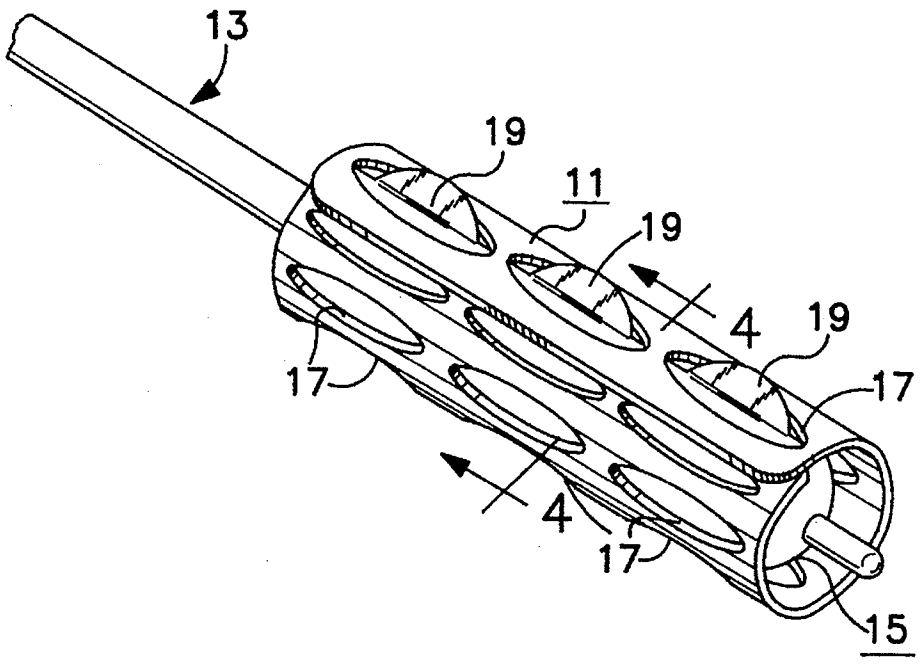
Primary Examiner—Paul B. Prebilic
Attorney, Agent, or Firm—John S. Munday; Stephen G. Stanton

[57] **ABSTRACT**

A minimally invasive bioactivated endoprosthesis device for vessel repair. The device comprises a stent which is formed from metal or polymers into a predetermined shape which may include a plurality of holes patterned with a desired size, shape and number. The stent is then coated with a polymer or is formed from a polymer which contains a bioactive substance which achieves an equilibrium with the surrounding body tissues or fluids, with the equilibrium being controlled by charge distribution, concentration and molecular weight of the bioactive substance in relation to the pore size of the polymeric carrier for controlled prolonged release of said bioactive substance. The bioactive substance may be selected from the group of heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein by-products, antifibrosis agents, hyaluronte, cyclosporine and mixtures of these bioactive substances for simultaneous multiple treatments. The stent itself may take several distinct configurations. Preferred is a stent which comprises a substructure selected from flat sheets, flat sheets having holes therein, meshes and stent frames having a sheath thereon, and the substructure is coated with a polymer embedded with a bioactive substance. The stent may be either self-expandable or mechanically expandable, such as by a balloon or other device.

11 Claims, 3 Drawing Sheets



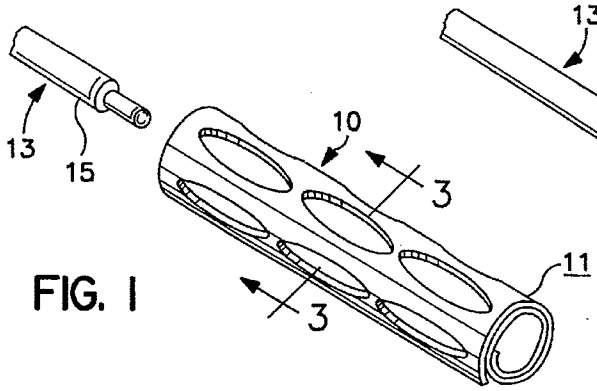


FIG. 1

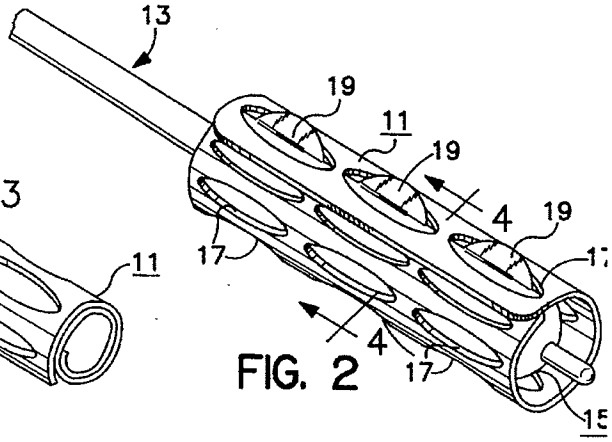


FIG. 2

FIG. 3

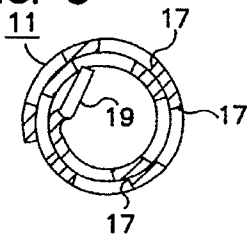


FIG. 4

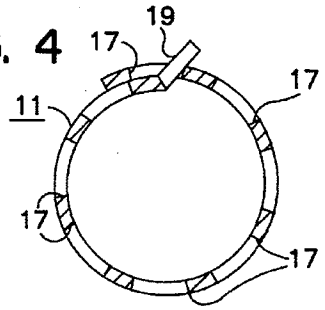


FIG. 6

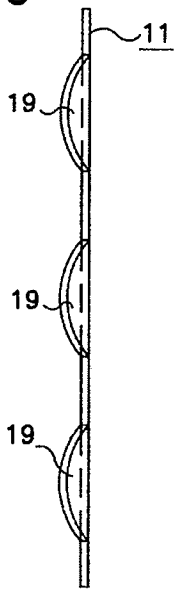


FIG. 5

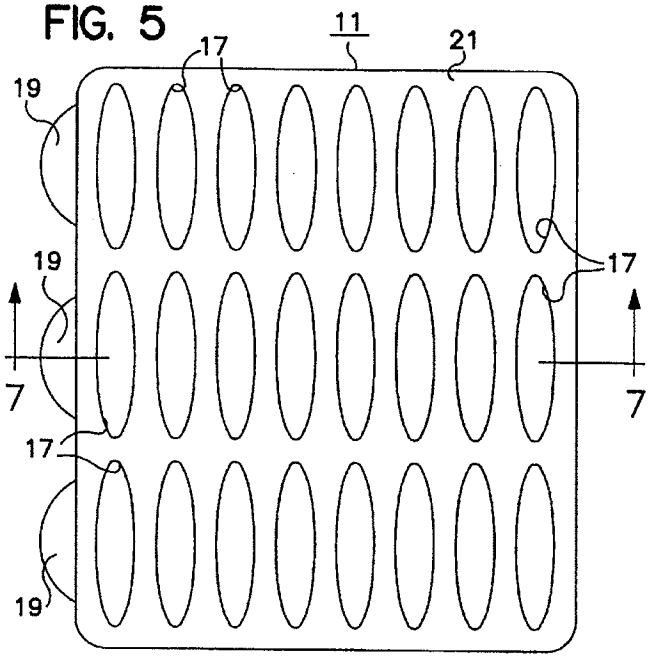


FIG. 7

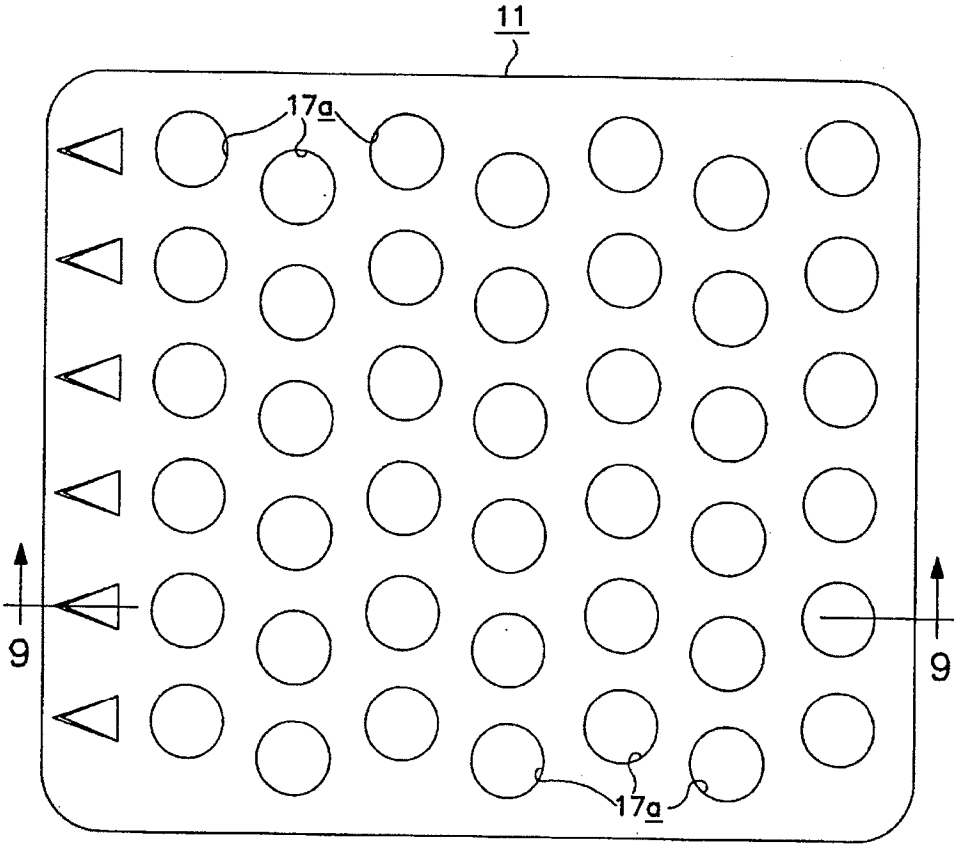


FIG. 8

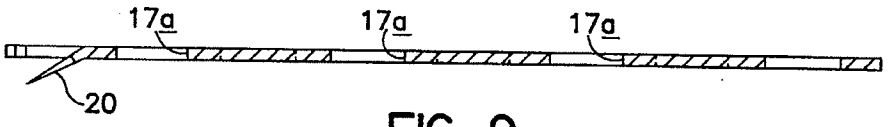


FIG. 9

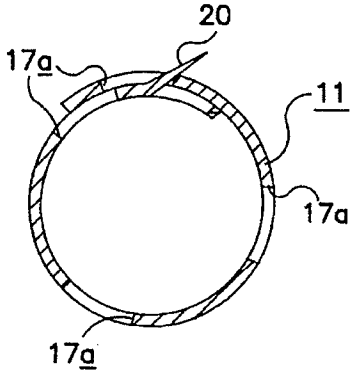


FIG. 10

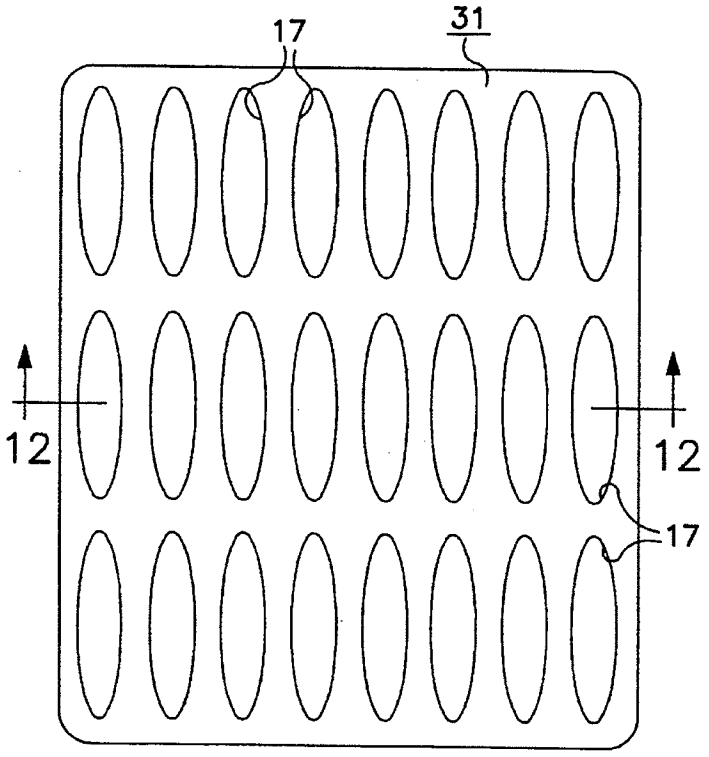


FIG. 11

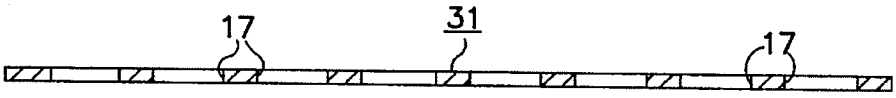


FIG. 12

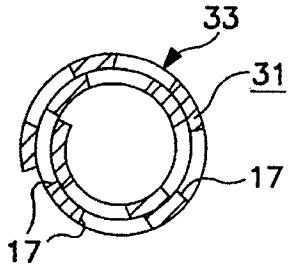


FIG. 13

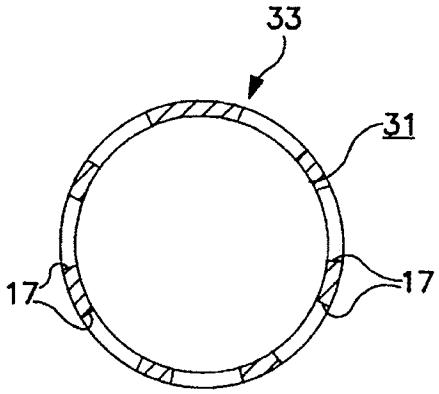


FIG. 14

MINIMALLY INVASIVE BIOACTIVATED ENDOPROSTHESIS FOR VESSEL REPAIR

This is a continuation-in-part of my prior application filed Mar. 2, 1994, having Ser. No. 08/204,947, now U.S. Pat. No. 5,449,382, which in turn is a continuation of my prior application filed Nov. 4, 1992, having Ser. No. 07/971,217, now abandoned.

FIELD OF THE INVENTION

The present invention relates to an improved percutaneously inserted endoprosthesis device which is permanently or temporarily implanted within a body vessel, typically a blood vessel. More particularly, the present invention relates to a new procedure for administering localized bioactive substances via prostheses designs which are adapted to resist problems associated with restenosis, thrombosis, infection calcification and/or fibrosis after implantation.

BACKGROUND OF THE INVENTION

In certain medical treatment procedures, a type of endoprosthesis device known as a stent is placed or implanted within a blood vessel for treating various problems such as stenonses, strictures, or aneurysms in the blood vessel. These devices are implanted within the vascular system to reinforce collapsing, partially occluded, weakened or abnormally dilated sections of the blood vessel. Stents may also be implanted in the ureter, urethra, bile duct, or any body vessel which has been narrowed, weakened or in any of the other ways which requires reinforcement.

A common approach for implanting stents in peripheral or coronary arteries is to first open the constricted region of the vessel via a percutaneous transluminally inserted angioplasty balloon catheter. The uninflated balloon at the tip of the catheter is advanced into the narrowed portion of the vessel lumen. The balloon is inflated so as to push the stenotic plaque outward, thereby enlarging the luminal diameter. Thereafter another catheter containing the stent is advanced to the region just enlarged by the balloon catheter and the stent is deployed. The catheter is withdrawn leaving the stent within the vessel.

The concept of implanting transluminally placed coil spring stents within an artery is not new. In one experiment in 1969, six stents were implanted in arteries of dogs. Three stents were stainless steel covered with silicone rubber and the other three stents were bare stainless steel. All three silicone coated stents occluded within 24 hours while two of the three bare stents remained open for thirty months. The stents were deployed using a pusher catheter having the same outer diameter as the stent.

In 1983, thermally expandable stents were reported, in which an alloy wire was shaped at thigh temperature into a stent configuration. Later it was straightened at room temperature into a configuration suitable for transluminal placement. Once placed within the vessel the stent was exposed to elevated temperatures to cause the alloy to return to its initial coil configuration. Canine studies of these stents, using the alloy nitinol, an alloy of nickel and titanium, demonstrated restenosis and intimal thickening 8 weeks following implant.

In 1984, self-expanding stents were described in which a device was introduced percutaneously after torsion reduction and was deployed by applying a reverse torsion in-vivo. This type of device proved to be complex and limited by a small expansion ration. Another self-expanding stent used

stainless steel wire in a zig zag configuration which resulted in incomplete vascular contact and only partial healing of the device. Yet another mechanical self-expanding stent was reported where a woven multifiliment stainless steel stent was deployed by a catheter with a constricting outer sleeve. Once in place, the outer sleeve was removed allowing self-expansion of the spring stent against the vessel wall.

Thrombosis occurred in these early prototypes, especially when the vessel tapered, and at branch points and at low expansion ratios. Canine aortic implantation resulted in multiple areas of vessel-to-stent adhesion at 3 weeks following implant. The stent exhibited minimal thrombogenicity.

Balloon expandable stents were first reported as being constructed of woven stainless steel wire where the cross points were silver soldered to resist radial collapse. The stent was deployed unexpanded over a balloon catheter, and once in position the stent was expanded by the outward force of the balloon. 8 of 11 stents implanted remained open for 1 to 8 weeks. It has been observed that the amount of intimal hyperplasia to be inversely proportional to the initial vessel lumen diameter. In another version, silver soldering cross points were replaced by the use of a stainless steel tube with rows of offset slots which became diamond shaped spaces. Although neointimal hyperplasia was observed, all stents remained open in rabbit aortas for 6 months.

Placement of a stent in a blood vessel is described in Lindemann et al U.S. Pat. No. 4,878,906 where a combination of sheath covered sleeve and a balloon catheter are used to locate and place the prosthesis. No recognition is given to the problems just discussed herein.

A prosthesis system using an expandable insert is shown in Garza et al U.S. Pat. No. 4,665,918, which is typical of those devices which are implanted without any express concern for the biocompatibility of the device being inserted. One can expect many of the foregoing problems and concerns to be evidenced by this device.

One device which is shown in U.S. Pat. No. 4,768,507 to Fischell et at describes a coil spring stent on which an application of a carbon coating or a carbon coated polytetrafluoroethylene has been applied on the surface of the coil spring. Fischell et al teaches that the thrombogenic potential of the device is reduced, through a passive methodology, but does nothing to address the biological response to the implant as a foreign body. Moreover, no suggestion is made of a way to inhibit neointimal hyperplasia, which inevitably follows balloon catheter induced injury to arterial vessels.

Yasuda U.S. Pat. No. 4,994,298 employs plasma polymerization to form a thin flexible coating on stents, teaching that improved biocompatibility, such as non-thrombogenicity and tissue or blood compatibility may be improved. Again this process is a passive methodology as previously described.

There are essentially two types of stents which have been employed in the prior art. Spring like stents have been inserted using a sheath or restraining element to keep the spring from expanding until It is in place. The other form of stent uses a method of expanding the stent once it is in place, such as a balloon catheter, Kreamer U.S. Pat. No. 4,740,207 describes one version of the balloon catheter version. In this patent, a semi-rigid tube which has a smaller relaxed diameter which is expanded to a larger operating diameter which Is maintained by a retaining ledge on the Inside of the graft. Concern here, of course, is that the inside located ledge and other retaining means may inadvertently function to cause further blockage of the tube once it is installed. Also.

Kreamer states that the tube is held in place by friction between the outer periphery of the graft and the inner periphery of the vessel to prevent displacement of the grant once in place In the vessel. The obvious concern is that the size must be precise or the tube will expand too much or too little, either damaging the vessel or escaping from the location for which it was intended.

Prior art devices represent a foreign body that has no biologically active properties and thus are a factor which contributes in a major way to the eventual restenosis or thrombosis of the vessel. These prior art devices attempt to reduce neointimal hyperplasia passively by adjusting mechanical variables such as lowering the stent profile, coating the stent with carbon, or by making the stent more or less rigid or flexible.

Accordingly, it is an object of the present invention to provide a device and method for deploying stents in blood vessels and other regions of the body without concern for the precise size of the stent being employed or the size of the vessel being treated or repaired.

It is an important object of this invention to produce a stent device and delivery system for the stent which produces rapid endothelialization with the least mount of intimal hyperplasia. While this goal has been stated by others, no effective method or device has been proposed to accomplish that goal.

Another object of this invention is to provide an endoprosthesis device and method for its use in which problems associated with restenosis, thrombosis, infection calcification and/or fibrosis after implantation may be avoided.

Yet another object of the present invention is to provide a device which is effective in administering localized bioactive substances to prevent rejection and side effects from an implanted endoprosthesis device.

Other objects will appear hereinafter.

SUMMARY OF THE INVENTION

It has now been discovered that the above and other objects of the present invention may be accomplished in the following manner. Specifically, an minimally invasive bioactivated endoprosthesis for vessel repair has been discovered which is admirably suited for long term use in a variety of surgical procedures and treatments.

The device is intended for use in those medical treatment procedures where a type of endoprosthesis device known as a stent is placed or implanted within a blood vessel for treating various problems such as stenonses, strictures, or aneurysms in the blood vessel. These devices may also be implanted within the vascular system to reinforce collapsing, partially occluded, weakened or abnormally dilated sections of the blood vessel. Stents of the present invention may also be implanted in the ureter, urethra, bile duct, or any body vessel which has been narrowed, weakened or in any of the other ways which requires reinforcement.

The device comprises a minimally invasive bioactivated endoprosthesis device for vessel repair, including a stent which is formed from metal or polymers into a predetermined shape which includes a plurality of holes patterned with a desired size, shape and number to provide a desired bending modulus. The stent may be fabricated from stainless steel, nitinol or other appropriate metallic alloys or may be formed from a variety of polymers which are known to be suitable for use with the human body.

When a metallic stent is employed, it is formed and then coated with a polymer which contains a bioactive substance which achieves an equilibrium with the surrounding body tissues or fluids, with the equilibrium being controlled by charge distribution, concentration and molecular weight of the bioactive substance in relation to the pore size of the polymeric carrier. Among these polymers are polymers having a microporous structure, such as silicone, polyurethane, polyvinyl alcohol, polyethylene, biodegradable polylactic acid polymers, polyglycolic acid polymers, polyesters, hydrogels, tetrafluroethylene and polytetrafluroethylene, fluorosilicone, hyaluronte and combinations, copolymers and blended mixtures thereof.

If the stent is formed from a polymer, these same polymeric materials may be employed, although some may need to be structurally reinforced. Also useful as a polymeric stent is polymethylmethacrylate, which is an example of the generic class of structurally adequate polymers without reinforcement.

A bioactive substance is preferably admixed in the polymer for elution from the microporous structure of the stent or coating on the stent after implantation. The rate of elution of the bioactive substance is controlled by selecting a pore size for the microporous structure in response to the concentration and molecular weight of the bioactive substance to achieve equilibrium between the polymer and the tissue or fluids proximate the stent upon implant. This permits a controlled and prolonged release of the bioactive substance as the polymer eluded or when a bioresorbable polymer erodes to release the bioactive substance.

The bioactive substance may be selected from the group of heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein by-products, antifibrosis agents, cyclosporine, hyaluronte and mixtures of these bioactive substances for simultaneous multiple treatments.

The stent itself may take several distinct configurations, all of which have a predetermined biasing force acting on the diameter of the stent. A flat, rectangular strip of stent material is formed, with the size being determined by the size of the blood vessel or other body conduit where the stent will be placed. As previously set forth, the strip includes a plurality of holes patterned with a desired size, shape and number to provide a desired bending modulus. Locking tabs are provided to engage the some of the plurality of holes at the maximum expanded size to prevent return to the smaller diameter coiled shape.

Preferred is a rolled stent which is provided with a coiled shape to which it tends to return when expanded. This is accomplished by using the same edge of the strip on which the tabs are formed as a rotational axis to roll the strip into a tight coil so that the tabs are in the center of the coil. Heat is applied to cause the strip to take a set in this coiled shape, so that when the coiled strip is radially expanded or unrolled, the form stresses will bias the strip to roll back into the preferred shape. The tabs which have been formed on what is now the inside edge will engage the holes formed in the strip and prevent collapse to the biased shape. Since a plurality of holes are formed in the strip, the device may be expanded to different sizes, depending upon the particular vessel in which it is placed. Under some circumstances, the device is capable of assuming a stent shape with more than one diameter, for the first time in these applications.

Alternatively the predetermined bias of the stent may be the expanded size so that the stent is coiled against this bias

during insertion. Holes are still placed in the sheet or strip to encourage adoption of the stent by the vessel. However, the relaxed or unbiased position is that of the intended final shape, and therefore locking tabs are not necessary. The stent is compressed or rolled to a smaller diameter prior to use with a built in bias to return to the "in use" shape previously built into the stent. This embodiment is installed using an introducer sheath. A balloon catheter may or may not be needed in view of the built in bias.

BRIEF DESCRIPTION OF THE DRAWINGS

For a more complete understanding of the invention, reference is hereby made to the drawings, in which:

FIG. **1** is an isometric view of an endoprosthesis for vessel repair.

FIG. **2** is an isometric view of the device shown in FIG. **1** in the most fully opened position.

FIG. **3** is a sectional view taken on line 3,3 of FIG. **1**.

FIG. **4** is a sectional view taken on line 4,4 of FIG. **2**.

FIG. **5** is a plan view development of the endoprosthesis blank prior to formation.

FIG. **6** is an end view of the device of FIG. **5** as viewed from the left hand side.

FIG. **7** is a sectional view taken on line 7,7 of FIG. **5**.

FIG. **8** is a plan view development of a second embodiment for an endoprosthesis blank.

FIG. **9** is a sectional view taken on line 9,9 of FIG. **8**.

FIG. **10** is a sectional view similar to FIG. **4** but showing the endoprosthesis formed from the blank of FIG. **8**.

FIG. **11** is a plan view development of a third embodiment for an endoprosthesis blank.

FIG. **12** is a sectional view taken along line 12,12 of FIG. **11**.

FIG. **13** is a sectional view similar to FIG. **4** but showing the endoprosthesis formed from the blank of FIG. **11**.

FIG. **14** is a view of the endoprosthesis of FIG. **13** after insertion and expansion in its position of intended use.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

As shown in the drawings, the device of this invention comprises a minimally invasive bioactivated endoprosthesis device, **10** generally, for vessel repair in contact with surrounding body tissues or fluids. The device includes a stent **11** which may be installed in the vessel using a catheter **13**, and in some cases using a balloon **15** on the end of catheter **13**. Stent **11**, which contains a plurality of holes **17**, is shown in a tightly coiled pre-insertion position in FIG. **1** with a fragment of balloon catheter **13** shown about to be inserted medially within the endoprosthesis. The sectional view shown in FIG. **3** illustrates a tab **19** which does not engage any holes **17** and which is enclosed within the coiled stent **11**, as the stent is in its relaxed or steady state with no bias from external forces acting on the stent.

In FIG. **2**, the stent **11** is illustrated in its most fully opened and locked position, as expansion has been effected diametrically by means of the medially positioned balloon **13**. FIGS. **2** and **4** shows how the tab **19** engage holes **17** and prevent the stent from re-coiling upon itself to return to the position shown in FIG. **3**.

The direction of the catheter and the balloon define an axis for reference to the various stents shown herein as part of the present invention. FIG. **5** is a plan view development prior to tightening and assembly of the stent into the predetermined shape. The stent **11** comprises a flat, rectangular strip **21** of a size determined by the size of the blood vessel or other body conduit where stent **11** will be placed. Tabs **19** extend along one end of strip **21** and are angled, as shown in FIG. **7**. Strip **21** is coiled and biased to take a smaller diameter coiled shape, as tabs **19** engage some of the plurality of holes **17** at a maximum desired expanded size to prevent return to the smaller diameter coiled shape.

The coiled stent **11** is formed by using that edge of strip **21** on which the tabs **19** are formed as a rotational axis to roll the strip **21** into a tight coiled stent so that the tabs **19** are in the center so that when coiled strip **11** is radially unrolled to the position shown in FIG. **2**, the form stresses will bias the strip **21** to roll back into the preferred shape of FIG. **3**, and tabs **19** will engage holes **17** formed in strip **21**, so as to prevent collapse to the biased shape of FIG. **3**.

By using the same edge of the strip **21** on which the tabs **19** are formed as a rotational axis to roll the strip into a tight coil, tabs **19** are in the center of the coiled stent. Heat is applied to cause the strip to take a set in this coiled shape, so that when the coiled strip is radially expanded or unrolled, the form stresses will bias the strip to roll back into the preferred shape. Tabs **19** which have been formed on what is now the inside edge will engage the holes **17** formed in the strip and prevent collapse to the biased shape. Since a plurality of holes **17** are formed in the strip **21**, the device may be expanded to different sizes, depending upon the particular vessel in which it is placed. Under some circumstances, the device is capable of assuming a stent shape with more than one diameter.

A slightly different stent layout is shown in FIGS. **8–10**, in that tabs **19** are replaced with pointed tabs **20**. Again the coiled stent **11** is heated or otherwise biased to move to a collapsed or tightly coiled condition. Pointed tabs **20** engage holes **17** and prevent such recoiling. In addition, pointed tabs **20** engage the side walls of the blood vessel or other part of the anatomy where the stent has been deployed.

Turning now to FIGS. **11–14**, an alternative embodiment is shown in which a strip **31** is formed into the desired size and shape, with holes **17** being provided for flexibility and for engagement with the tissue after implantation in some instances. No tabs are needed for this embodiment since this stent will have an outward biasing tendency. The stent assumes the shape shown in FIG. **14** after heating or otherwise forming the rolled stent into a usable configuration. When implantation is desired, the stent **33** is constricted to a smaller diameter as shown in FIG. **13**, so that the bias of the design is to expand the stent. An introducter sheath of the type already in use should be used to position the stent in the vessel of choice. It may be only necessary to pull the sheath back to expose the stent.

In all of the devices of this invention, it is intended that a polymer form the exterior surface of the stent, either as a coating or as the stent itself. The drawings should be interpreted to understand that a polymer does form the exterior surface, whether or not a substrate such as a metal stent is used. The polymer should have a microporous structure with a predetermined pore size. Also included in the polymer is a bioactive substance having a charge distribution, concentration and molecular weight selected which achieves an equilibrium in relation to the pore size of the polymeric carrier with said surrounding body tissues or fluids.

Among these polymers are polymers having a microporous structure, such as silicone, polyurethane, poly-

vinyl alcohol, polyethylene, polyesters, hydrogels, tetrafluroethylene and polytetrafluoroethylene, fluorosilicone, hyaluronte and combinations, copolymers and blended mixtures thereof. One preferred resorbable polymer is biodegradable polylactic acid, and another is polyglycolic acid. These materials are suitable for being formed into a stent that possesses acceptable tensile strength characteristics.

If the stent is formed from a polymer, these same polymeric materials may be employed, although some may need to be structurally reinforced. Also useful as a polymeric stent is polymethylmethacrylate, which is an example of the generic class of polymers having good structural properties. In any event, the bioactive substance is incorporated into the polymer prior to insertion of the stent into the vessel.

Radio opaque substances such as, for example, fluorescein, may also be incorporated into the stent so as to assist in the deployment and subsequent evaluative follow-up of the surgery. A primary purpose of the bioactive substance is to inhibit vessel wall restenosis following vascular balloon angioplasty. In addition, stents of the present invention may be used to improve the diameter of the urethra or fallopian tubes, ureter, bile duct, trachea, esophagus, or other body vessel.

Preferred bioactive substances are heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein by-products, antifibrosis agents, cyclosporine, hyaluronte and mixtures of these bioactive substances for simultaneous multiple treatments. Of course, virtually any bioactive substance of need to the patient is a possible agent for treating the patient, depending upon the needs of the treatment.

The preparation of the stents of this invention is as follows. When a metallic stent is contemplated, and any of these stent designs may benefit from the concepts of this invention, a medical grade of polymer is selected. Preferred is a silicone elastomer. A quantity of silicone elastomer is mixed in a 3 to 1 ration with ethyl ether to form a solution suitable for coating a metallic stent. A quantity of bioactive substance required to achieve the desired therapeutic effect is admixed with the polymer and ethyl ether solution. After thorough blending, the now bioactivated polymer solution is ready to be used to coat the stent.

The cleaned metallic stent is coated by the bioactivated polymer using a variety of methods. One method is to completely submerge or dip the stent into a quantity of polymer so that the metallic stent is fully covered. After coating and removing from the dip, the polymer is cured or vulcanized at the desired temperature, depending upon the polymer. Alternatively, the polymer may be sprayed on to the polymer and then cured. Yet another method includes pouring a coating over the stent while the stent is being rotated. Plasma coating is also effective.

A variety of stent designs may be employed within the scope of the present invention as defined above. In one embodiment, the stent may take the form of a metallic wire stent. Alternatively the stent may be a metallic tube with alternating slots which form a wire-like mesh when expanded. The stent may be self-expanding or balloon expanded. With this stent a polymer embedded with a bioactive substance is used to cover the wire, leaving the space between the wire or mesh uncovered. Alternatively the polymer embedded with a bioactive substance may be used to cover the wire or mesh and fill in the spaces between the wires, thereby maximizing the polymer in contact with surrounding tissues. In both cases tissue ingrowth is permitted to encourage and facilitate rapid endothelialization, either with the spaces between the wires or in holes formed in the outer surface of the polymer as drugs are released to permit tissue ingrowth. Yet another embodiment would be to coat the outer surface of a fabric or other sheath material which is then used in combination with a metallic stent frame.

In addition, the stents described with respect to FIGS. **1–14** may be modified so that a flat sheet with multiple holes, such as stent **11** of FIGS. **1–4**, with holes **17** but without tab **19**. In this embodiment the spring-like properties of sheet **21** are sufficient to cause stent **11** to unroll to the desired size. In this embodiment, the polymer embedded with a bioactive substance is used to cover the flat portion **21** of stent **11** without occluding holes **17**. Alternatively, holes **17** could also be covered by the polymer embedded with a bioactive substance as previously described with respect to a mesh stent and release of drugs from the outer surface of the polymer embedded with a bioactive substance will leave additional holes to permit and encourage tissue ingrowth.

In yet another embodiment, the flat sheet or mesh configuration may be composed entirely of polymer that is formed into the desired stent configuration directly without an accompanying substructure. The stent thus formed may be comprised of a polymer that is permanent, to give a long term structural support as the drugs are eluted, or the polymer may be biodegradable so that in time, as the treatment succeeds and tissue heals and rebuilds itself, the polymer will be absorbed by the body. Of course, long term treatment by the drugs within the polymer takes place in either case.

Finally, an additional embodiment is contemplated in which the polymer embedded with a bioactive substance is cured in situ at the diseased site so as to structurally support the vessel while treating the tissues via polymeric release. In this method, the non-cured polymer is injected into the vessel site via a catheter so as to 'coat' the surrounding vessel walls. The polymer is cured within the vessel to form a tubular layer or lining in direct contact with the surrounding tissues. As the drug is released, holes are again formed to permit ingrowth as has been described herein, particularly where the polymer is non-resorbable. When resorbable polymers are used to form the in-situ cured stent, tissue quickly displaces the polymer as it biodegrades, this permitting endothelialization.

While particular embodiments of the present invention have been illustrated and described, it is not intended to limit the invention, except as defined by the following claims.

I claim:

1. A minimally invasive bioactivated endoprosthesis device for vessel repair in contact with surrounding body tissues, comprising:

a stent formed from a solid non-biodegradable material presenting a substantial surface to said tissues for use with a blood vessel or other body conduit to form an internally unrestricted stent having a diameter of a selected size for said blood vessel or other body conduit; said stent including a plurality of holes sufficiently large to permit rapid endothelialization; and

a polymer forming at least the exterior surface of said stent for direct polymer to tissue contact with said tissue, said polymer having a porous structure with a predetermined pore size and further including a bioactive substance within said pores for elution from said pores, said pore size being selected in response to the

concentration and molecular weight of said substance to achieve equilibrium between said polymer and said tissue to provide a controlled and prolonged release of said bioactive substance to said surrounding body tissue in an amount sufficient to substantially prevent hyperplasia or therapeutically treat said tissue, said stent having sufficient amount of said substantial surface to support a quantity of said polymer capable of prolonged release of said amount.

2. A method of making a minimally invasive bioactivated endoprosthesis device for vessel repair in contact with surrounding body tissues, comprising the steps of:

forming a stent from a non-biodegradable material sized to present a substantial surface to said tissues for use with a blood vessel or other body conduit and having a diameter of a selected size for said blood vessel or other body conduit; said material including a plurality of holes sufficiently large to permit rapid endothelialization; and

forming a polymer on at least the exterior surface of said stent for direct polymer to tissue contact with said tissues, said polymer having a porous structure with a predetermined pore size and further including a bioactive substance within said pores for elution from said pores, said pore size being selected in response to the concentration and molecular weight of said substance to achieve equilibrium between said polymer and said tissues to provide a controlled and prolonged release of said bioactive substance to said surrounding body tissues in an amount sufficient to substantially prevent hyperplasia or therapeutically treat said tissues, said stent having a sufficient amount of said substantial surface to support a quantity of said polymer capable of prolonged release of said amount.

3. The device of claim **1**, wherein said stent comprises a substructure selected from the group consisting of flat sheets, flat sheets having holes therein, meshes and stent flames having a sheath thereon; said structure being coated with said polymer embedded with a bioactive substance.

4. The device of claim **1**, wherein said stent is formed in-situ from said polymer embedded with a bioactive substance wherein the polymer is cured after placement in contact with surrounding tissues.

5. The device of claim **1**, wherein said stent comprises a metallic substructure having said polymer as a coating.

6. The device of claim **1** wherein said polymer is selected from the group of silicone, polyurethane, polyvinyl alcohol, polyethylene, biodegradable polylactic acid polymers, polyglycolic acid polymers, polyesters, hydrogels, polytetrafluroethylene, fluorosilicone, hyaluronte and combinations, copolymers and blended mixtures thereof.

7. The device of claim **1**, wherein said bioactive substance is selected from the group consisting of heparin, hirudin, prostacyclenes or analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal antibodies, snake venom protein by-products, antifibrosis agents, hyaluronte, cyclosporine and mixtures of these bioactive substances for simultaneous multiple treatments.

8. The device of claim **1** wherein said stent is formed solely from said polymer having sufficient structural integrity to be formed into a stent.

9. The method of claim **2**, wherein said stent is formed from a substructure selected from the group consisting of flat sheets, flat sheets having holes therein, meshes and stent frames having a sheath thereon; said structure being coated with said polymer embedded with a bioactive substance.

10. The method of claim **2**, wherein said stent is formed in-situ from a polymer embedded with a bioactive substance wherein the polymer is cured after placement in contact with surrounding tissues.

11. The method of claim **2**, wherein said stent is selected from the group consisting of self-expanding and mechanically expandable stents.

* * * * *

US005578075B1

REEXAMINATION CERTIFICATE (3992nd)

United States Patent [19] [11] **B1 5,578,075**

Dayton [45] Certificate Issued ***Feb. 8, 2000**

[54] **MINIMALLY INVASIVE BIOACTIVATED ENDOPROSTHESIS FOR VESSEL REPAIR**

[75] Inventor: **Michael P. Dayton**, Tampa, Fla.

[73] Assignee: **Daynke Research, Inc.**, Tampa, Fla.

Reexamination Request:
No. 90/005,278, Mar. 1, 1999

Reexamination Certificate for:
Patent No.: **5,578,075**
Issued: **Nov. 29, 1996**
Appl. No.: **08/457,850**
Filed: **Jun. 1, 1995**

[*] Notice: This patent is subject to a terminal disclaimer.

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/204,947, Mar. 2, 1994, Pat. No. 5,449,382, which is a continuation of application No. 07/971,217, Nov. 4, 1992, abandoned.

[51] **Int. Cl.**[7] **A61F 2/06**

[52] **U.S. Cl.** **623/1**; 6223/12; 6223/901; 604/104; 604/107

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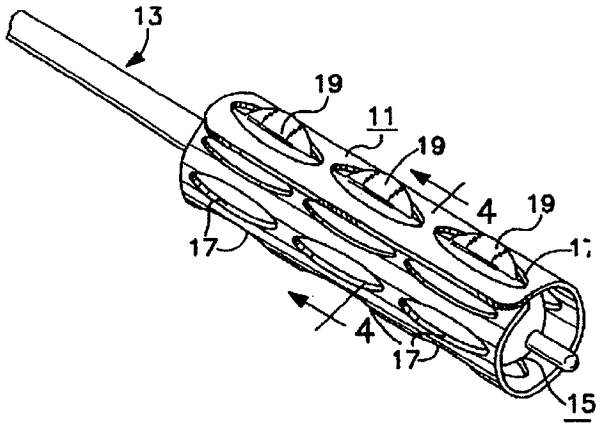
Primary Examiner—Paul Prebilic

[57] **ABSTRACT**

A minimally invasive bioactivated endoprosthesis device for vessel repair. The device comprises a stent which is formed from metal or polymers into a predetermined shape which may include a plurality of holes patterend with a desired size, shape and number. The stent is then coated with a polymer or is formed from a polymer which contains a bioactive substance which achieves an equilibrium with the surrounding body tissues or fluids, with the equilibrium being controlled by charge distribution, concentration and molecular weight of the bioactive substance in relation to the pore size of the polymeric carrier for controlled prolonged release of said bioactive substance. The bioactive substance may be selected from the group of heparin, hirudin, prostacyclenes and analogs thereof, antithrombogenic agents, steroids, ibuprofen, antimicrobials, antibiotics, tissue plasma activators, rifamicin, monoclonal, antibodies, snake venom protein by-products, antifibrosis agents, hyaluronte, cyclosporine and mixtures of these bioactive substances for simultaneous multiple treatments. The stent itself may take several distinct configurations. Preferred is a stent which comprises a substructure selected from flat sheets, flat sheets having holes therein, meshes and stent frames having a sheath thereon, and the substructure is coated with a polymer embedded with a bioactive substance. The stent may be either self-expandable or mechanically expandable, such as by a balloon or other device.



REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1, 2,** and **4–11** is confirmed.

Claim **3** is determined to patentable as amended.

3. The device of claim **1**, wherein said stent comprises a substructure selected from the group consisting of flat sheets, flat sheets having holes therein, meshes and stent **[**flames**]** *frames* having a sheath thereon; said structue being coated with said polymer embedded with a bioactive substance.

* * * * *

US005624411A

United States Patent [19]

Tuch

[11] Patent Number: 5,624,411

[45] Date of Patent: Apr. 29, 1997

[54] **INTRAVASCULAR STENT AND METHOD**

[75] Inventor: **Ronald J. Tuch**, Plymouth, Minn.

[73] Assignee: **Medtronic, Inc.**, Minneapolis, Minn.

[21] Appl. No.: **483,005**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 52,878, Apr. 26, 1993, Pat. No. 5,464,650.

[51] **Int. Cl.**[6] **A61M 29/00**

[52] **U.S. Cl.** **604/265**

[58] **Field of Search** 604/28, 92–93, 604/83, 51–53, 48–49, 891.1, 264–266; 606/191–194; 600/36; 623/1, 12

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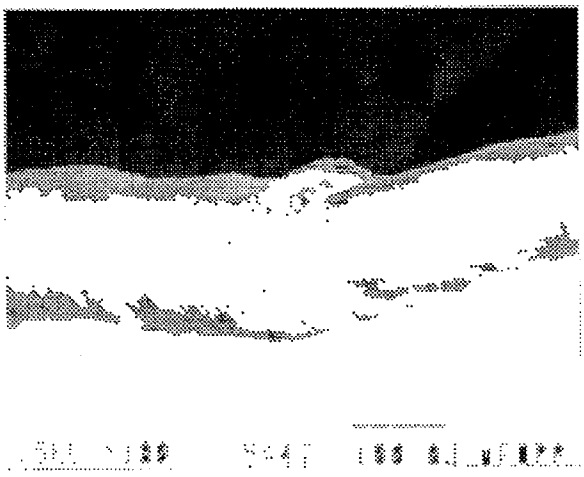
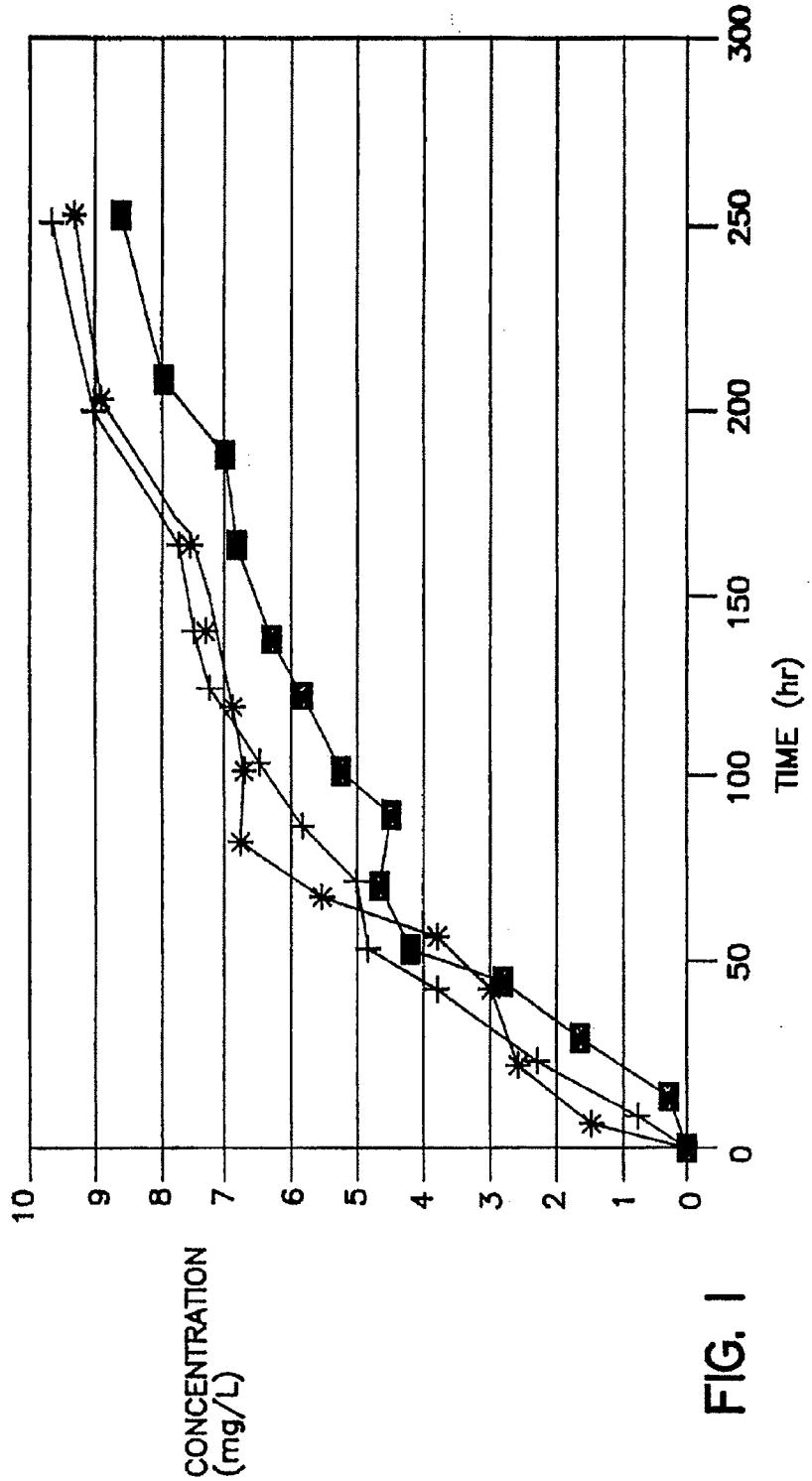
Primary Examiner—Randall L. Green
Assistant Examiner—Perry E. Van Over
Attorney, Agent, or Firm—Daniel W. Latham; Harold R. Patton

[57] **ABSTRACT**

A method for making an intravascular stent by applying to the body of a stent a therapeutic substance and then overcoating the therapeutic substance with a porous polymer. The inclusion of a porous polymer in intimate contact with a drug on the stent allows the drug to be retained on the stent during expansion of the stent and also controls the administration of drug following implantation. The adhesion of the coating and the rate at which the drug is delivered can be controlled by the selection of an appropriate bioabsorbable or biostable polymer.

27 Claims, 5 Drawing Sheets

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9
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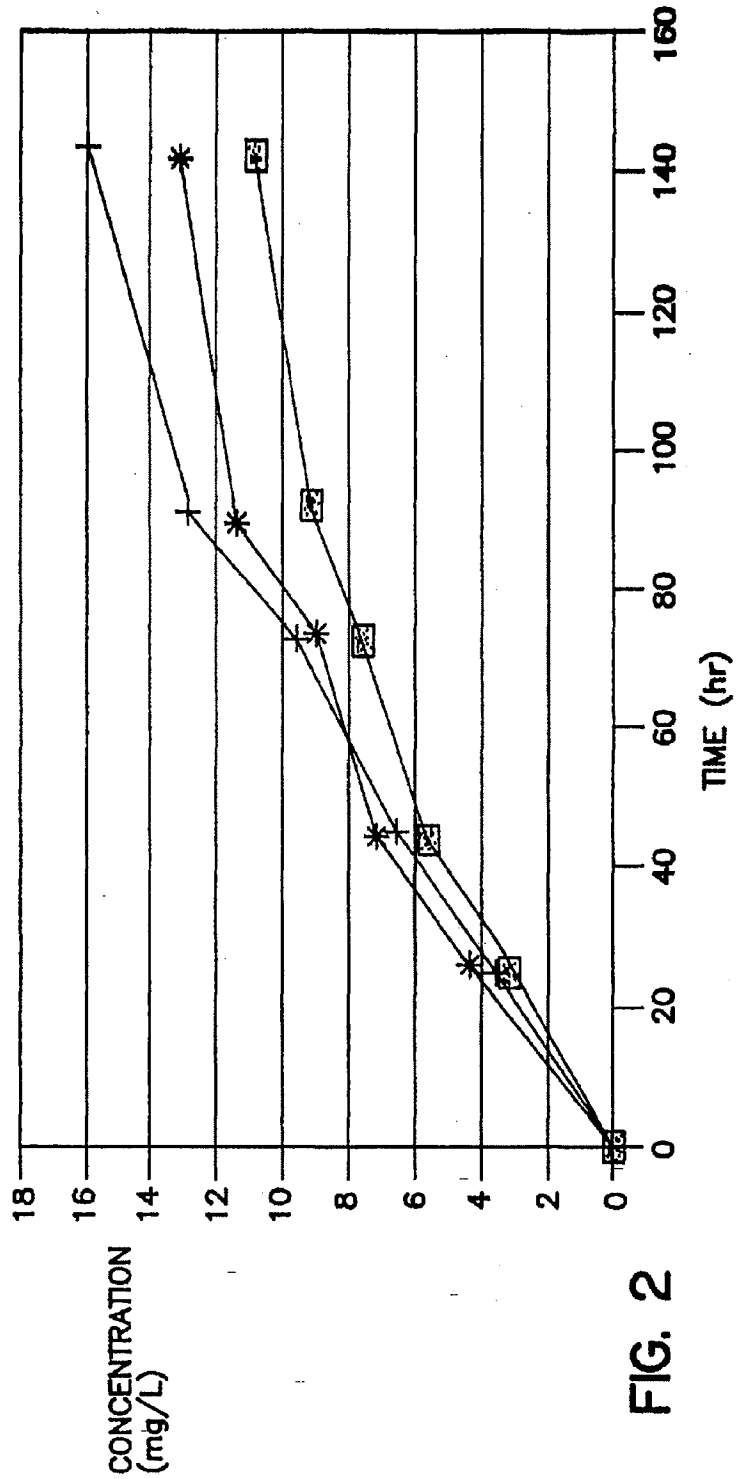
200
250
300

FIG. 1


CONCENTRATION (mg/L)
18
16
14
12
10
8
6
4
2
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40
60
80
100
120
140
160

FIG. 2

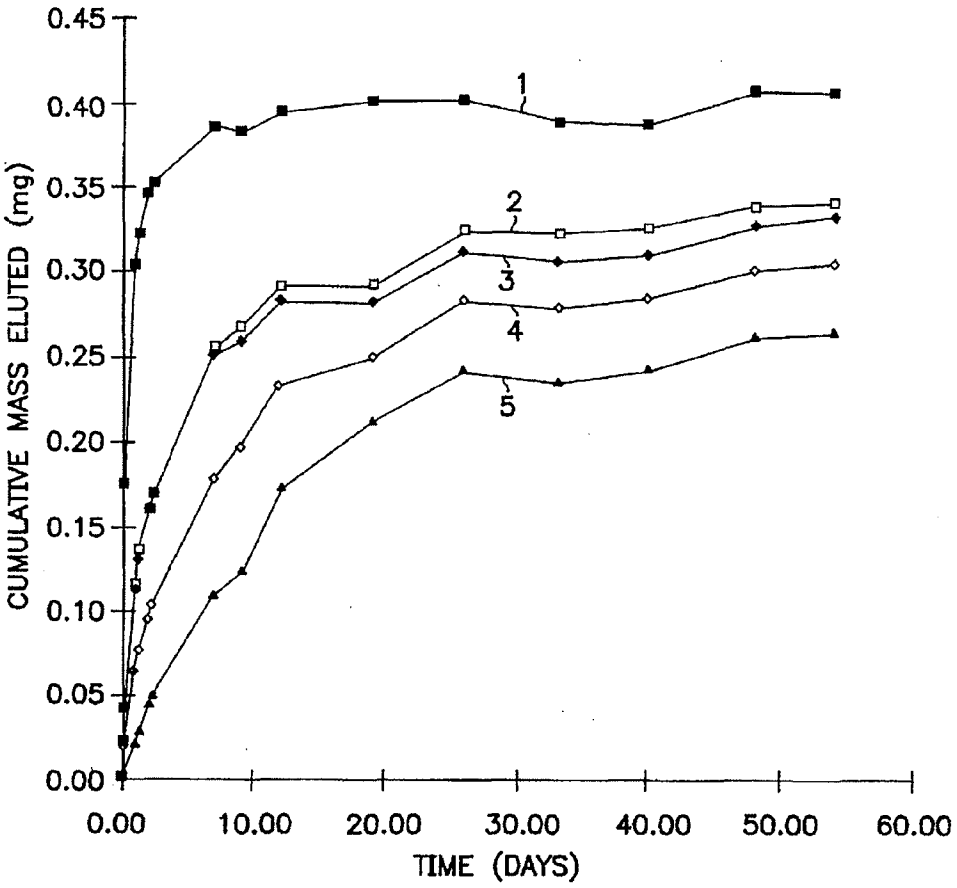
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
CUMULATIVE MASS ELUTED (mg)
0.00
10.00
20.00
30.00
40.00
50.00
60.00
TIME (DAYS)
1
2
3
4
5

FIG. 3

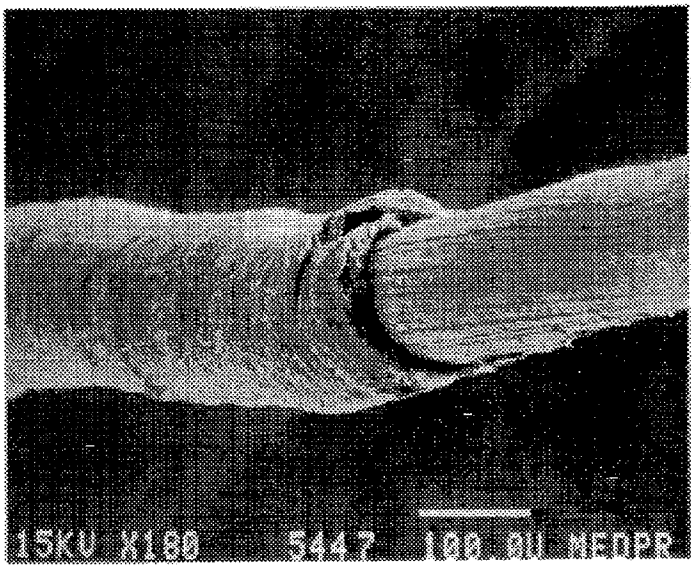

Fig. 4a

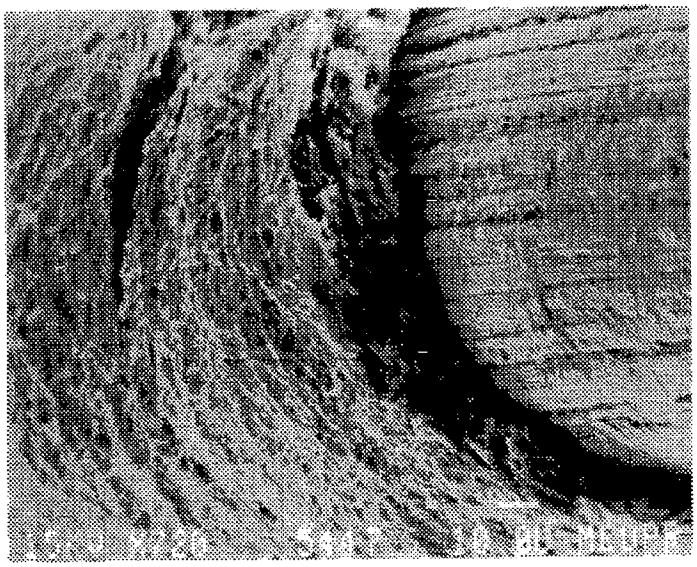

Fig. 4b

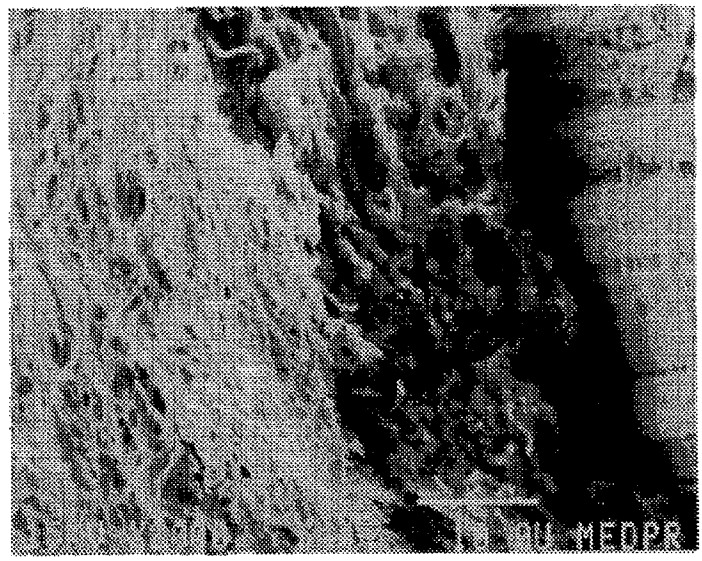

Fig. 4c

INTRAVASCULAR STENT AND METHOD

This is a continuation-in-part of Ser. No. 08/052,878 filed Apr. 26, 1993 now U.S. Pat. No. 5,464,650.

BACKGROUND OF THE INVENTION

This invention relates to intravascular stents for treatment of injuries to blood vessels and particularly to stents having a framework onto which a therapeutic substance or drug is applied.

Although angioplasty procedures have increased greatly in popularity for treatment of occluded arteries, the problem of restenosis following the angioplasty treatment remains a significant problem. Restenosis is the closure of a peripheral or coronary artery following trauma to the artery caused by efforts to open an occluded portion of the artery by angioplasty, such as, for example, by balloon dilation, atherectomy or laser ablation treatment of the artery. For these angioplasty procedures, restenosis occurs at a rate of about 30–60% depending upon the vessel location, lesion length and a number of other variables.

One aspect of restenosis may be simply mechanical; e.g. caused by the elastic rebound of the arterial wall and/or by dissections in the vessel wall caused by the angioplasty procedure. These mechanical problems have been successfully addressed by the use of stents to tack-up dissections and prevent elastic rebound of the vessel, thereby reducing the level of restenosis for many patients. The stent is typically inserted by catheter into a vascular lumen and expanded into contact with the diseased portion of the arterial wall, thereby providing internal support for the lumen. Examples of stents which have been successfully applied over a PTCA balloon and radially expanded at the same time as the balloon expansion of an affected artery include the stents disclosed in U.S. Pat. Nos. 4,733,665 issued to Palmaz, 4,800,882 issued to Gianturco and 4,886,062 issued to Wiktor which are incorporated herein by reference in their entirety.

Another aspect of restenosis is believed to be a natural healing reaction to the injury of the arterial wall that is caused by angioplasty procedures. The final result of the complex steps of the healing process is intimal hyperplasia, the migration and proliferation of medial smooth muscle cells, until the artery is again occluded.

To address both aspects of the restenosis problem, it has been proposed to provide stents which are seeded with endothelial cells (Dichek, D. A. et al Seeding of Intravascular Stents With Genetically Engineered Endothelial Cells; Circulation 1989; 80:1347–1353). In that experiment, sheep endothelial cells that had undergone retrovirus-mediated gene transfer for either bacterial beta-galactosidase or human tissue-type plasminogen activator were seeded onto stainless steel stents and grown until the stents were covered. The cells were therefore able to be delivered to the vascular wall where they could provide therapeutic proteins. Other methods of providing therapeutic substances to the vascular wall include simple heparin-coated metallic stents, whereby a heparin coating is ionically or covalently bonded to the stent. Still other methods of providing therapeutic substances to the vascular wall by means of stents have also been proposed such as in U.S. Pat. No. 5,102,417 issued to Palmaz or in international patent application WO 91/12779 "Intraluminal Drug Eluting Prosthesis" and international patent application WO 90/13332 "Stent With Sustained Drug Delivery". In those applications, it is suggested that antiplatelet agents, anticoagulant agents, antimicrobial agents, antimetabolic agents and other drugs could be supplied in stents to reduce the incidence of restenosis.

Metal stents such as those disclosed in U.S. Pat. Nos. 4,733,665 issued to Palmaz, 4,800,882 issued to Gianturco or 4,886,062 issued to Wiktor could be suitable for drug delivery in that they are capable of maintaining intimate contact between a substance applied to the outer surface of the stent and the tissues of the vessel to be treated. However, there are significant problems to be overcome in order to secure a therapeutically significant amount of a substance onto the metal of the stent; to keep it on the stent during expansion of the stent into contact with the blood vessel wall; and also controlling the: rate of drug delivery from the drug on the stent to the vessel wall.

It is therefore an object of the present invention to provide a stent having a therapeutically significant amount of a drug applied thereto.

It is also an object of the present invention to provide a stent which may be delivered and expanded in a selected blood vessel without losing a therapeutically significant amount of a drug applied thereto.

It is also an object of the present invention to provide a drug-containing stent which allows for a sustained release of the drug to vascular tissue.

It is also an object of the present invention to provide a simple method for applying to a stent a coating of a therapeutic substance.

SUMMARY OF THE INVENTION

These and other objects are accomplished by the present invention. We have discovered an intravascular stent including a coating which includes a polymer and a therapeutic substance on the body of a stent, and in particular on its tissue-contacting surface, in which the coating includes a porous polymeric overlayer. The inclusion of a polymer in intimate contact with a drug on the stent allows the drug to be retained on the stent in a resilient matrix during expansion of the stent and also slows the administration of drug following implantation. By including a porous overlayer in the coating, the concentration of drug is greatest toward the stent body so that control over the rate of administration of the drug is significantly improved. Also, the porosity of the overlayer is believed to provide improved resistance to cracking as the stent is radially expanded or contracted which makes timed delivery, of drug more certain. The coating can be applied whether the stent has a metallic or polymeric surface. The coating can also be provided by methods which assure carefully controlled dosage.

In one aspect of the invention, the coating includes as an underlayer a drug and polymer applied by simply immersing the stent into a solution of the drug and polymer or by spraying the solution onto the stent. This coating can be provided as a solid/solid solution of the drug and polymer by dissolving the drug and polymer in a common solvent or as a dispersion of drug in the polymer. The total amount of drug to be included on the stent can be readily controlled by applying multiple thin coats of the solution while allowing it to dry between coats. For example, a target dosage of drug is determined and the stent body is weighed. A solution of polymer, drug and solvent having a predetermined weight ratio of polymer to drug is applied to the stent body in successive thin coats with drying and weighing of the stent between coats. When the total weight of coating on the stent multiplied by the weight ratio of drug in the coating indicates that the target dosage has been achieved, no additional drug/polymer solution is applied. The overall coating should

be thin enough so that it will not significantly increase the profile of the stent for intravascular delivery by catheter. It is therefore preferably less than about 0.002 inch thick and most preferably less than 0.001 inch thick. The adhesion of the coating and the rate at which the drug is delivered can be controlled by the selection of an appropriate bioabsorbable or biostable polymer and by the ratio of drug to polymer in the solution. By this method, drugs such as glucocorticoids (e.g. dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, ACE inhibitors, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents can be applied to a stent, retained on a stent during expansion of the stent and elute the drug at a controlled rate.

The release rate of the drug is further controlled by the porous overlayer. For example, such a coating includes a higher drug-to-polymer ratio in the inner layers than in the outer layers of the coating which would result in a lower initial dose and a total dose which would be delivered more evenly and over a much longer period of time. This can be accomplished while maintaining the correct therapeutic dosage by applying to a stent which already has a coating containing a desired amount of drug, a thin coating overlayer or several thin overlayers of the same polymer and solvent without the drug while drying the stent between each coating layer.

In another aspect of the invention, the coating need not be an applied mixture of polymer and drug, but may instead be provided by a drug applied to the stent from aqueous solution or dispersion. For example, heparin can be applied from aqueous solution onto the stent body and allowed to dry. The porous polymeric overcoating can then be applied to the heparin coated stent body such that it controls the release of heparin from the coating. In yet another aspect of the invention, the surface concentration of drug on the stent can be adjusted by varying the hydrophilicity/hydrophobicity of the base to which the aqueous drug coating is applied. For example, in a tantalum stent, a coating of a hydrophobic polymer can be applied to the stent as an underlayer to receive the aqueous drug. When applied to this surface, the aqueous solution of drug forms beads of drug on some portions of the stent surface while other portions of the surface are relatively free of the drug. The porous overlayer can then be applied over the polymeric underlayer and beads of drug to encapsulate the beads of drug and secure them to the stent surface. If a more uniform surface is desired, a hydrophilic polymer can be applied as an underlayer or the polymeric underlayer can be provided with a plasma treatment to introduce hydrophilic chemical groups onto the polymer surface.

In operation, the stent made according to the present invention can deliver drugs to a body lumen by introducing the stent transluminally into a selected portion of the body lumen and radially expanding the stent into contact with the body lumen. The transluminal delivery can be accomplished by a catheter designed for the delivery of stents and the radial expansion can be accomplished by balloon expansion of the stent, by self-expansion of the stent, or a combination of self-expansion and balloon expansion.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a plot showing elution profiles for stents with a coating of dexamethasone and poly(L-lactic acid) made according to Example 6.

FIG. **2** is a plot showing elution profiles for sterilized stents with a coating of dexamethasone and poly(L-lactic acid) made according to Example 7.

FIG. **3** is a graph showing elution profiles for stents coated with colchicine and poly(L-lactic acid) which have an overlayer of poly(L-lactic acid).

FIGS. **4***a*–**4***c* are SEM micrographs of a porous poly(L-lactic acid) overlayer applied to a stent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for making an intravascular stent. The underlying structure of the stent can be virtually any stent design, whether of the self-expanding type or of the balloon-expandable type and whether metal or polymeric. Thus metal stent designs such as those disclosed in U.S. Pat. Nos. 4,733,665 issued to Palmaz, 4,800,882 issued to Gianturco or 4,886,062 issued to Wiktor could be used in the present invention. The stent could be made of virtually any bio-compatible material having physical properties suitable for the design. For example, tantalum and stainless steel have been proven suitable for many such designs and could be used in the present invention. Also, stents made with biostable or bioabsorbable polymers such as poly(ethylene terephthalate), polyacetal, poly(lactic acid), poly(ethylene oxide)/poly(butylene terephthalate) copolymer could be used in the present invention. Although the stent surface should be clean and free from contaminants that may be introduced during manufacturing, the stent surface requires no particular surface treatment in order to retain the coating applied in the present invention. Both the inner and outer surfaces of the stent may be provided with the coating according to the present invention.

In order to provide the first layer of the coated stent, a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent is first prepared. It is important to choose a solvent, a polymer and a therapeutic substance that are mutually compatible. It is essential that the solvent is capable of placing the polymer into solution at the concentration desired in the solution. It is also essential that the solvent and polymer chosen do not chemically alter the therapeutic character of the therapeutic substance. However, the therapeutic substance only needs to be dispersed throughout the solvent so that it may be either in a true solution with the solvent or dispersed in fine particles in the solvent. Examples of some suitable combinations of polymer, solvent and therapeutic substance are set forth in Table 1 below.

TABLE 1

POLYMER	SOLVENT	THERAPEUTIC SUBSTANCE
poly(L-lactic acid)	chloroform	dexamethasone
poly(L-lactic acid)	chloroform	colchicine
poly(lactic acid-co-glycolic acid)	acetone	dexamethasone
polyether urethane silicone adhesive	N-methyl pyrrolidone xylene	tocopherol (vitamin E) dexamethasone phosphate
poly(hydroxy-butyrate-co-hydroxyvalerate)	dichloro-methane	aspirin
fibrin	water (buffered saline)	heparin

The solution is applied to the stent and the solvent is allowed to evaporate, thereby leaving on the stent surface a

coating of the polymer and the therapeutic substance. Typically, the solution can be applied to the stent by either spraying the solution onto the stent or immersing the stent in the solution. Whether one chooses application by immersion or application by spraying depends principally on the viscosity and surface tension of the solution, however, it has been found that spraying in a fine spray such as that available from an airbrush will provide a coating with the greatest uniformity and will provide the greatest control over the amount of coating material to be applied to the stent. In either a coating applied by spraying or by immersion, multiple application steps are generally desirable to provide improved coating uniformity and improved control over the amount of therapeutic substance to be applied to the stent.

The polymer chosen must be a polymer that is biocompatible and minimizes irritation to the vessel wall when the stent is implanted. The polymer may be either a biostable or a bioabsorbable polymer depending on the desired rate of release or the desired degree of polymer stability, but a bioabsorbable polymer is probably more desirable since, unlike a biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Bioabsorbable polymers that could be used include poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly (glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly (trimethylene carbonate), poly(iminocarbonate), copoly (ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, biostable polymers with a relatively low chronic tissue response such as polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

The ratio of therapeutic substance to polymer in the solution will depend on the efficacy of the polymer in securing the therapeutic substance onto the stent and the rate at which the coating is to release the therapeutic substance to the tissue of the blood vessel. More polymer may be needed if it has relatively poor efficacy in retaining the therapeutic substance on the stent and more polymer may be needed in order to provide an elution matrix that limits the elution of a very soluble therapeutic substance. A wide ratio of therapeutic substance to polymer could therefore be appropriate and could range from about 10:1 to about 1:100.

The therapeutic substance used in the,, present invention could be virtually any therapeutic substance which possesses desirable therapeutic characteristics for application to a blood vessel. This can include both solid substances and liquid substances. For example, glucocorticoids (e.g. dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, ACE inhibitors, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents could be used. Antiplatelet agents cart include drugs such as aspirin and dipyridamole. Aspirin is classified as an analgesic, antipyretic, anti-inflammatory and antiplatelet drug. Dypridimole is a drug similar to aspirin in that it has anti-platelet characteristics. Dypridimole is also classified as a coronary vasodilator. Anticoagulant agents can include drugs such as heparin, coumadin, protamine, hirudin and tick anticoagulant protein. Antimitotic agents and antimetabolite agents can include drugs such as colchicine, methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin and mutamycin. Taking colchicine for example, colchicine is an ancient drug which was tested for restenosis reduction by systemic administration without favorable results (see O'Keefe, J. H., et al. "Ineffectiveness of Colchicine in the Prevention of Restenosis after Coronary Angioplasty," JACC 1992; 19(7); 1597–1600). Given its unsuccessful use in systemic administration, it was also tested by local administration with the stent coating of the present invention to determine its efficacy. Another noteworthy drug is heparin which is not soluble or dispersible in organic solvents like methylene chloride or chloroform but which can be applied from aqueous solution onto the stent body.

In order to provide additional control over the elution of the drug, an overlayer is also applied to the stent. The higher drug-to-polymer ratio in the inner layers than in the outer layers would result in a lower initial dose and a total dose which would be delivered more evenly and over a much longer period of time. In the solid/solid solution of polymer and drug of poly(L-lactic acid) and colchicine, this can be accomplished while maintaining the, correct therapeutic dosage by applying to a stent which already has a coating containing a desired amount of colchicine a thin coating layer or several thin overlayers of the same poly(L-lactic acid) polymer and chloroform solvent without the colchicine while drying the stent between each coating layer. Since both the, colchicine and poly(L-lactic acid) are soluble in the chloroform, the colchicine and poly(L-lactic acid) already on the stent body are dissolved slightly in the application of each of the coating overlayers which creates a concentration gradient of colchicine in the overlayers that is sharply reduced from that in the main coating nearest the stent body. The effect of this is to alter the drug delivery profile for the stent such as that shown in FIG. 3. In FIG. 3, a coating of 20% colchicine/poly(L-lactic acid) was coated with different overlayer thicknesses. In the curve given by reference numeral 1, an overlayer was provided only on one end of the stent. In the curve given by curve 2, an overlayer was given to the entire stent. In curve 3, the same coating thickness was applied as for curve 2 while in curves 4, and 5 coatings two times as thick and six times as thick respectively were applied. The effect of these overlayers was to dramatically decrease the rate at which the colchicine eluted such that the colchicine did not completely elute out of the stent after the first few days.

With an aqueous coating of drug on the stent, the polymer overlayer is even more important to the control of elution from the implanted stent. For example, an aqueous coating of heparin can be provided by spraying a solution or

dispersion of heparin onto the stent body. When the heparin layer is dry, a solution of chloroform and poly(L-lactic acid) can be used to form the overlayer in the same manner as disclosed above for the colchicine example.

Application of the aqueous drug solution or dispersion can be accomplished by spraying or immersing the stent and drying the resulting coating in essentially the same manner as for the application of polymer and drug disclosed above.

The overlayer described above can be provided in porous form. Contrary to expectations, it has been found that the porous overlayer can reduce rather than increase the rate of drug elution. While not wishing to be bound by theory, it is believed that the porous overlayer is less susceptible to cracking as the stent undergoes deformation during handling and implantation. For example, with a Wiktor type stent, the coating is applied to a stent which is in an expanded form. Once the coating is dried, the stent is crimped onto a delivery balloon which causes various stent elements and the coating to bend. During implantation, the delivery balloon expands, again deforming the stent elements and coating. In a very uniform overlayer made with materials which have little elasticity, the overlayer can sustain significant cracking during such deformation. These cracks can then act as channels for more rapid elution of drugs from the drug-rich base coating.

A suitable porous coating can be provided, for example, by phase inversion precipitation of the polymer in the overlayer. According to this technique, a solution of a polymer is prepared in a mixture of two miscible solvents, one of which being a poorer solvent for this polymer and less volatile than the other solvent. When the solution is allowed to dry, there becomes a moment when the good solvent has sufficiently evaporated for causing the polymer to slowly precipitate which results, after complete drying, in an opened porous structure. For example, when using poly(L-lactic acid) as the polymer, a suitable solvent composition can include about a 40/60% (w/w) isooctane/chloroform solution. This solution should be mixed carefully to avoid precipitation during the mixing process. The better solvent for the polymer should dissolve the polymer first (i.e. a solution of poly(L-lactic acid) and chloroform should be made first). A mixture of the solvents should then be added to the polymer solution to bring the ingredients to the desired concentration (i.e. a mixture of isooctane and chloroform is added to the poly(L-lactic acid) solution). This mixture is then applied to the stent in the same manner as set forth above. It will be appreciated by those skilled in the art that the nature of the ingredients and the relative concentrations of the ingredients will determine the size of pores. Pores in the range of about 0.5 to 10 microns in diameter may be suitable. Phase inversion precipitation techniques are well known in the manufacture of porous polymeric membranes. (See e.g. van de Witte et al, *Polyactide Membranes: Correlation between phase transitions and morphology*, doctoral thesis, CIP-GEGEVENS KONINKLUKE BIBLIOTHEEK, DEN HAAG, 1994). A porous coating may also result under less controlled conditions from application of the overlayer during high humidity conditions in which atmospheric moisture condenses on the stent due to localized cooling of the stent as the solvent evaporates.

The following examples are exemplary of various aspects of the invention.

EXAMPLE 1

A 1% solution of dexamethasone in acetone was made, forming a clear solution. The solution was placed in an airbrush reservoir (Badger #200). Wiktor type tantalum wire stents were sprayed with the solution in short bursts while rotating the stents. The acetone quickly evaporated from the stents, leaving a white residue on the stent wire. The process was continued until all of the stent wires were coated. The drug elution rate for the stent was determined by immersing the stent in phosphate buffered saline solution (pH=7.4). Traces of dexamethasone were observed to remain on the immersed stents for less than 31 hours.

EXAMPLE 2

A 2% solution of dexamethasone in acetone was made, forming a solution with suspended particles of dexamethasone. The solution was placed into a tube. Wiktor type tantalum wire stents were dipped rapidly and were allowed to dry. Each stent was dipped into the solution 12–15 times to provide a white surface coating. Two stents were placed on an angioplasty balloon and were inflated on the balloon. Approximately 80% of the dexamethasone coating flaked-off of the stents.

EXAMPLE 3

A solution of 1% dexamethasone and 0.5% poly (caprolactone) (Aldrich 18,160-9) in acetone was made. The solution was placed into a tube. Wiktor type tantalum wire stents were dipped rapidly and were allowed to dry. Each stent was dipped into the solution 12–15 times to provide a white surface coating. A stent so coated was expanded on a 3.5 mm angioplasty balloon causing a significant amount of the coating to become detached.

EXAMPLE 4

A solution of 1% dexamethasone and 0.5% poly(LACTIC ACID-CO-GLYCOLIC ACID) (Medisorb) in acetone was made. The solution was placed into a tube. Wiktor type tantalum wire stents were dipped rapidly and were allowed to dry. Each stent was dipped into the solution 12–15 times to provide a white surface coating. A stent so coated was expanded on a 3.5 mm angioplasty balloon causing only a small portion of the coating (less than 25%.) to become detached)

EXAMPLE 5

A solution including a 2% dispersion of dexamethasone and a 1% solution of poly(L-lactic acid) (CCA Biochem MW=550.000) in chloroform was made. The solution was placed into an airbrush (Badger). Wiktor type tantalum wire stents were sprayed in short bursts and were allowed to dry. Each stent was sprayed with the solution about 20 times to provide a white surface coating. A stent so coated was expanded on a 3.5 mm angioplasty balloon. The coating remained attached to the stent throughout the procedure.

EXAMPLE 6

A solution including a 2% dispersion of dexamethasone and a 1% solution of poly(L-lactic acid) (CCA Biochem MW=550.000) in chloroform was made. The solution was placed into an airbrush (Badger #250-2). Wiktor type tantalum wire stents were suspended from a fixture and sprayed in 24 short bursts (6 bursts from each of the four directions perpendicular to the stent axis) and were allowed to dry. The resulting stents had a coating weight of about 0.0006–0.0015 grams. Three of the stents were tested for long term elution by placing one stent in 3.0 ml of phosphate buffered saline solution (pH=7.4) at room temperature without stirring. The

amount of dexamethasone eluted was evaluated by measuring absorbance at 244 nm in a UV-VIS spectrophotometer. The results of this test are given in FIG. 1.

EXAMPLE 7

A solution including a 2% dispersion of dexamethasone and a 1% solution of poly(L-lactic acid) (Medisorb 100-L) in chloroform was made along with a control solution of 1% of poly(L-lactic acid) (Medisorb 100-L) in chloroform. The solutions was placed into an airbrush (Badger #250-2). Wiktor type tantalum wire stents were expanded on a 3.0 mm balloon, suspended from a fixture and sprayed in 16 short bursts (2–3 bursts of about 1 second followed by several minutes drying time between applications). The resulting dexamethasone,-coated stents had an average coating weight of about 0.0012 grams while the polymer-coated stents had an average polymer weight of about 0.0004 grams. The stents were sterilized in ethylene oxide. Three of the sterilized dexamethasone-coated stents were tested for long term elution by placing one stent in 3.0 ml of phosphate, buffered saline solution (pH=7.4) at room temperature without stirring. The amount of dexamethasone eluted was evaluated by measuring absorbance at 244 nm in a UV-VIS spectrophotometer. The results of this test are given in FIG. 2. Dexamethasone-coated stents and polymer-coated control stents were implanted in the coronary arteries of 8 pigs (N=12 for each type) according to the method set forth in "Restenosis After Balloon Angioplasty—A Practical Proliferative Model in Porcine Coronary Arteries," by Robert S. Schwartz, et al, *Circulation* 82(6):2190–2200, Dec. 1990, and "Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: Results in a Porcine Model" by Robert S. Schwartz et al, *J Am Coll Cardiol;* 19;267–74 Feb. 1992 with the result that when compared with the controls, the dexamethasone-coated stents reduced the amount of proliferation associated with the arterial injury.

EXAMPLE 8

Stents were coated with colchicine and poly(L-lactic acid)formulations for in vivo testing. Solutions of poly(L-lactic acid) and colchicine in chloroform were prepared and mixed to provide a desired percentage of colchicine in the coating with the poly(L-lactic acid) content of the solution maintained at about 1%. The solutions was placed into an airbrush (Badger #250-2). Wiktor type tantalum wire stents were expanded on a 3.0 mm balloon, suspended from a fixture and sprayed in short bursts (bursts of about 1 second). After an amount of colchicine had been applied to each stent, the stents were dried in air for at least about thirty minutes and then further dried in a vacuum drying oven at about 80° C. The stents were removed from the drying oven and weighed. Any difference between the target weight of colchicine to be applied to each stent and the actual weight of colchicine on the stent was noted and the number of additional bursts needed to bring each stent to target weight was estimated. Any weight-deficient stents were then brought up to target weight by the application of additional bursts of the solution. Any recoated stents were then dried and weighed again. A 1% solution of poly(L-lactic acid) in chloroform was used to provide an overlayer to the colchicine-coated stents. A desired number of bursts of the solution (i.e. bursts of about 1 second with preferably a drying time of about 4 seconds between bursts) was applied by spraying in the same manner as the application of the base coating and were dried and weighed. The average amounts of drug and overlayer are given in Table 2.

TABLE 2

Lot	% drug	Drug Mass (mg)	Overlayer Mass (mg)
1	35	1.39	0.78
2	25	1.03	2.42
3	25	0.58	1.29
4	15	0.21	1.16
5	10	0.10	0.55
6	15	0.21	1.22
7	10	0.10	0.61

The stents were then packaged and gas sterilized.

EXAMPLE 9

Stents were provided with an overlayer of porous poly (L-lactic acid) by a phase inversion precipitation technique. A 40/60% (w/w) isooctane/chloroform solution was used containing 0.5% poly(L-lactic acid). The solution was made by adding 2.0 g of a solution of 5.0% Poly(L-lactic acid) in chloroform to a pre-mixed solution of 8.0 g isooctane and 10.0 g chloroform. An airbrush apparatus (Badger #250-2) was used to apply the solution to Wiktor stents under the following conditions:

Air pressure=30 psi

Burst duration=0.5 second

Nozzle to stent distance=30 mm

Time between bursts=5–7 seconds (coating turns white)

Ambient temperature and humidity

Stents were rotated 5/16 of a turn after each burst and sprayed initially with 50 bursts/end. After at least 4 hours of air drying, the stents were fixtured at the other end and the second half was coated. After overnight vacuum drying at 80° C., the stents were weighed. Additional coatings were applied using the same conditions to bring each stent up to the target weight. The completed stents were vacuum dried at 80° C. for 7 days. The stents were tested for mechanical adhesion of the coating during crimping and expansion operations. The coating was finally fractured by straightening out the sinusoidal wave of the stent and the coating was pulled off with a tweezers to produce the SEM micrographs shown on FIGS. 4*a*–4*c* of the coating at 180X, 720X and 2000X respectively.

EXAMPLE 10

Stents were provided with a multi-layer heparin-eluting coating. A 1% solution of poly(L-lactic acid) in chloroform was used to provide an underlayer for the heparin-coated stents. This solution was applied by spraying onto the stents with an airbrush in substantially the same manner as set forth in the examples above such that thin underlayer was provided. A 2% heparin solution was prepared with sterile water. The heparin solution was applied with an airbrush. A poly(L-lactic acid) overlayer was then applied by airbrush from a 1% solution in chloroform. High humidity conditions caused the formation of a cloudy, porous overlayer. The amounts of material on each stent is given in Table 3.

TABLE 3

Stent	Stent Wt (g)	Underlayer (mg)	Heparin (mg)	Overlayer (mg)
1	0.02002	0.34	0.15	0.0
2	0.02006	0.35	0.17	0.26
3	0.02008	0.36	0.14	1.17

TABLE 3-continued

Stent	Stent Wt (g)	Underlayer (mg)	Heparin (mg)	Overlayer (mg)
4	0.02009	0.30	0.34	0.25
5	0.01993	0.35	0.40	1.11
6	0.01922	0.32	0.40	1.89
7	0.02001	0.52	0.73	0.31
8	0.01906	0.37	0.75	1.17
9	0.01901	0.42	0.70	2.07

Each stent was crimped onto an angioplasty balloon and expanded. Elution tests were run on the expanded stents in phosphate buffered saline solution with aliquots withdrawn at various times up to 44 days. Results were as set forth in Table 4.

TABLE 4

Stent	Units eluted	% Recovery	80% Elution (days)
1	26	94	0
2	21	65	2
3	10	40	18
4	50	78	1
5	48	64	18
6	38	51	28
7	131	96	1
8	121	86	18
9	111	85	18

It will be appreciated by those skilled in the art that while the invention has been described above in connection with particular embodiments and examples, the invention is not necessarily so limited and that numerous other embodiments, examples, uses, modifications and departures from the embodiments, examples and uses may be made without departing from the inventive concepts.

I claim:

1. A device for delivery of a drug into a body lumen comprising:

(a) a generally cylindrical, radially expandable stent body;

(b) a coating on the stent body a first coating layer comprising a therapeutic substance and a second coating layer comprising a porous polymer overlaying the first coating layer;

(c) means for introducing the stent body and coating transluminally into a selected portion of the body lumen; and

(d) means for radially expanding the stent into contact with the body lumen.

2. A device according to claim **1** wherein the stent body has a metal surface.

3. A device according to claim **1** wherein the stent body has a polymeric surface.

4. A device according to claim **1** wherein the polymer is a bioabsorbable polymer.

5. A device according to claim **4** wherein the polymer is selected from the group consisting of poly(lactic acid), poly(lactide-co-glycolide) and poly(hydroxybutyrate-co-valerate).

6. A device according to claim **1** wherein the polymer is a biostable polymer.

7. A device according to claim **6** wherein the polymer is selected from the group consisting of silicones, polyurethanes, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers and cellulosics.

8. A device according to claim **1** wherein the drug is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, anticoagulants, heparin, hirudin, tick anticoagulant peptide, angiopeptin, antimitotic agents, and oligonucleotides.

9. A device according to claim **1** in which the porous polymer has average pore diameter in the range of about 0.5–10 microns.

10. A method for delivery of a therapeutic substance to the interior of a body lumen comprising the steps of:

(a) providing a generally cylindrical stent body;

(b) providing as a coating on the stent body a first coating layer comprising a therapeutic substance and a second coating layer comprising a porous polymer overlaying the first coating layer;

(c) introducing the stent transluminally into a selected portion of the body lumen; and

(d) radially expanding the stent into contact with the body lumen.

11. A method according to claim **10** wherein the stent body has a metal surface.

12. A method according to claim **10** wherein the stent body has a polymeric surface.

13. A method according to claim **10** wherein the polymer is a bioabsorbable polymer.

14. A method according to claim **13** wherein the polymer is selected from the group consisting of poly(lactic acid), poly(lactide-co-glycolide) and poly(hydroxybutyrate-co-valerate).

15. A method according to claim **10** wherein the polymer and therapeutic agent are in a solid/solid solution.

16. A method according to claim **10** wherein the polymer is a biostable polymer.

17. A method according to claim **16** wherein the polymer is selected from the group consisting of silicones, polyurethanes, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers and cellulosics.

18. A method according to claim **10** wherein the drug is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, anticoagulants, heparin, hirudin, tick anticoagulant peptide, angiopeptin, antimitotic agents, and oligonucleotides.

19. A method for providing a stent having a therapeutic substance thereon comprising the steps of:

(a) providing a cylindrical, radially expandable stent body;

(b) applying to the stent body a solution which includes a solvent and a therapeutic substance dispersed in the solvent;

(c) evaporating the solvent;

(d) applying to the therapeutic substance on the stent body an overlayer of a polymer by the steps of:

(1) applying to the stent body a solution which includes a solvent and the polymer dissolved in the solvent;

(2) evaporating the solvent to produce pores in the resulting polymer coating; and

(e) radially expanding the stent body, applied polymer and therapeutic substance such that the polymer and therapeutic substance are retained on the stent body.

20. A method according to claim **19** wherein the overlayer is applied by spraying.

21. A method according to claim **19** wherein the overlayer is applied by immersion.

22. A method according to claim **19** wherein the polymer is a bioabsorbable polymer.

23. A method according to claim 22 wherein the polymer is selected from the group consisting of poly(lactic acid), poly(lactide-co-glycolide) and poly(hydroxybutyrate-co-valerate).

24. A method according to claim 19 wherein the polymer is a biostable polymer.

25. A method according to claim 24 wherein the polymer is selected from the group consisting of silicones, polyurethanes, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers and cellulosics.

26. A method according to claim 19 wherein the solution for applying the overlayer includes a solvent mixture, the solvent mixture including a first solvent in which the polymer has a solubility and a second solvent in which the polymer has a lesser solubility.

27. A method according to claim 19 wherein the drug is selected from the group consisting of glucocorticoids, dexamethasone, dexamethasone sodium phosphate, anticoagulants, heparin, hirudin, tick anticoagulant peptide, angiopeptin, antimitotic agents, and oligonucleotides.

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United States Patent [19]

Ding et al.

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[54] **DRUG RELEASE STENT COATING PROCESS**

[75] Inventors: **Ni Ding**, Plymouth, Minn.; **Michael N. Helmus**, Long Beach, Calif.

[73] Assignee: **Schneider (USA) Inc**, Plymouth, Minn.

[21] Appl. No.: **663,490**

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[51] **Int. Cl.**[6] **B05D 3/00**; A61L 27/00; A61L 33/00

[52] **U.S. Cl.** **427/2.21**; 427/2.25; 623/12

[58] **Field of Search** 427/2.21, 2.25; 623/1, 11, 12

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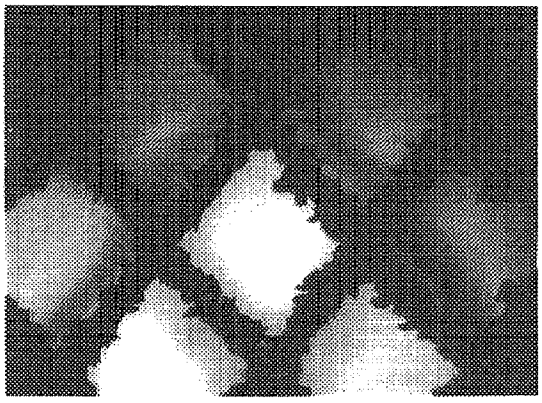
Primary Examiner—Erma Cameron
Attorney, Agent, or Firm—Pennie & Edmonds LLP

[57] **ABSTRACT**

A method of coating implantable open lattice metallic stent prosthesis is disclosed which includes sequentially applying a plurality of relatively thin outer layers of a coating composition comprising a solvent mixture of uncured polymeric silicone material and crosslinker and finely divided biologically active species, possibly of controlled average particle size, to form a coating on each stent surface. The coatings are cured in situ and the coated, cured prosthesis are sterilized in a step that includes preferred pretreatment with argon gas plasma and exposure to gamma radiation electron beam, ethylene oxide, steam.

18 Claims, 7 Drawing Sheets



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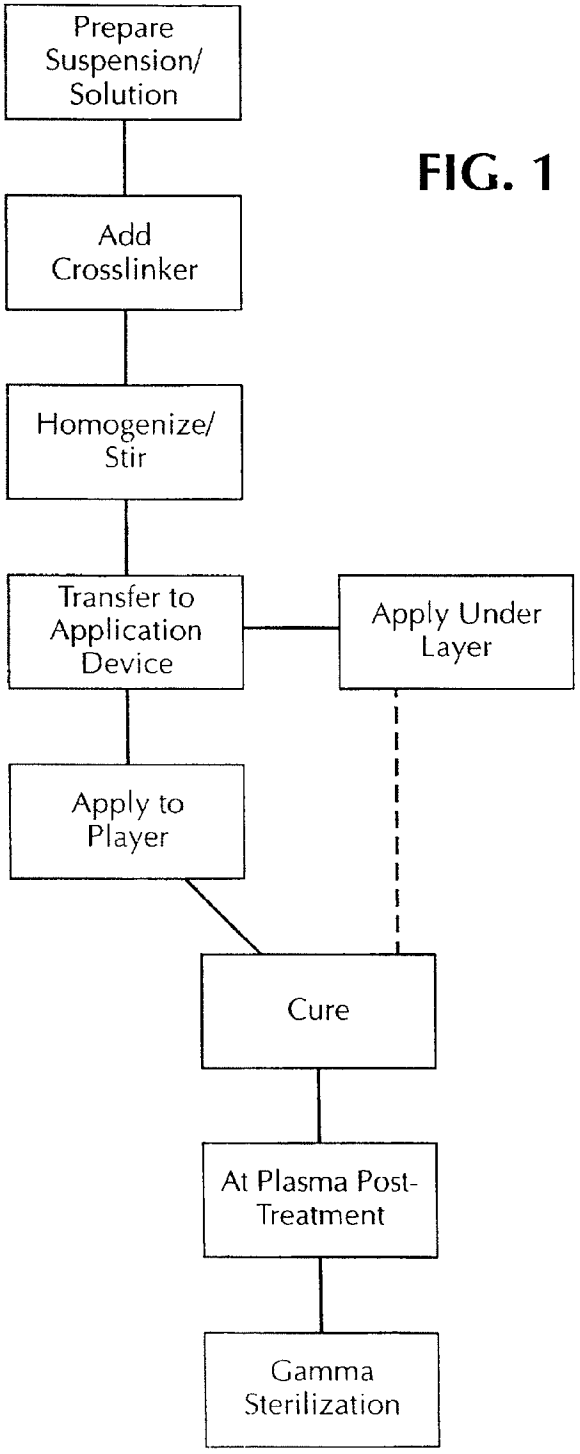

Prepare Suspension/ Solution
Add Crosslinker
Homogenize/ Stir
Transfer to Application Device
Apply Under Layer
Apply to Player
Cure
At Plasma Post-Treatment
Gamma Sterilization

FIG. 1

FIG. 2

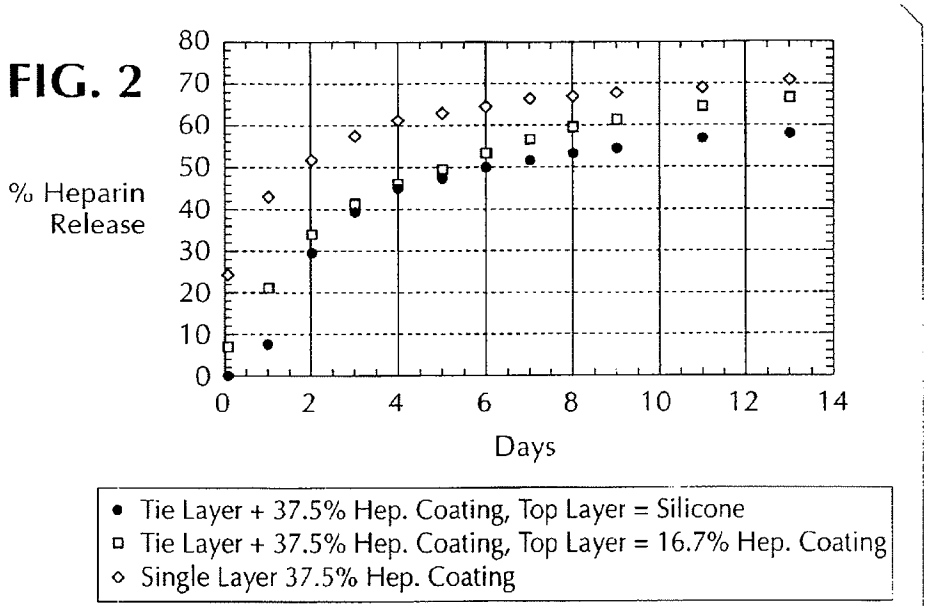

% Heparin Release
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
Days
• Tie Layer + 37.5% Hep. Coating, Top Layer = Silicone
□ Tie Layer + 37.5% Hep. Coating, Top Layer = 16.7% Hep. Coating
◇ Single Layer 37.5% Hep. Coating

FIG. 3

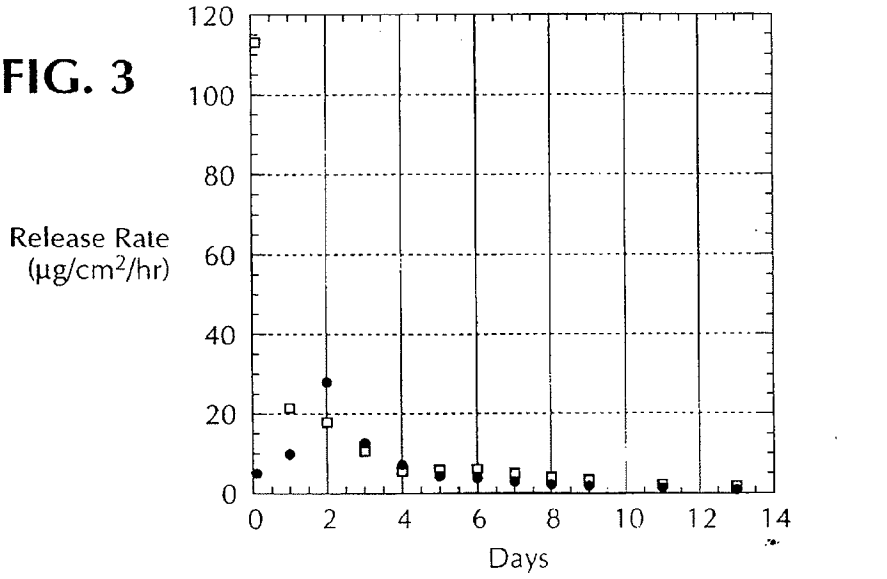

Release Rate (μg/cm²/hr)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Days
• Tie Layer + 37.5% Hep. Coating, Top Layer = Silicone
□ Tie Layer + 37.5% Hep. Coating, Top Layer = 16.7% Hep. Coating

FIG. 4

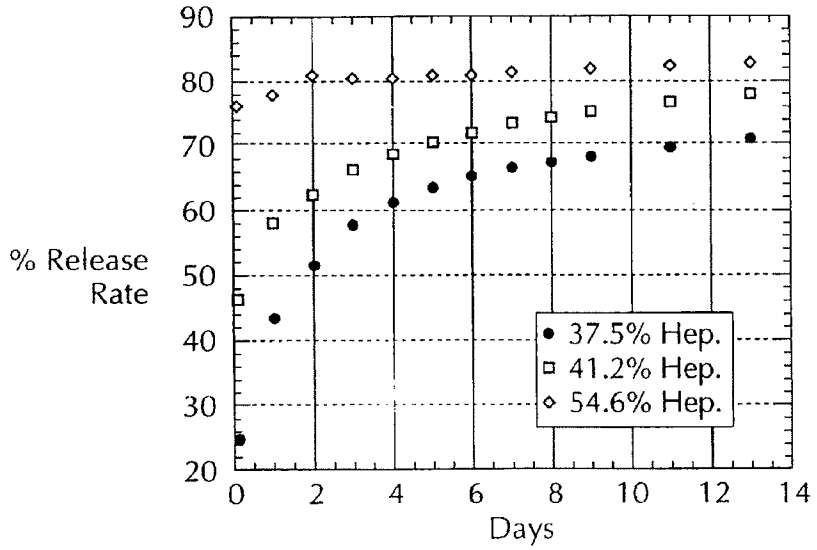

% Release Rate
90
80
70
60
50
40
30
20
0
2
4
6
8
10
12
14
Days
37.5% Hep.
41.2% Hep.
54.6% Hep.

FIG. 5

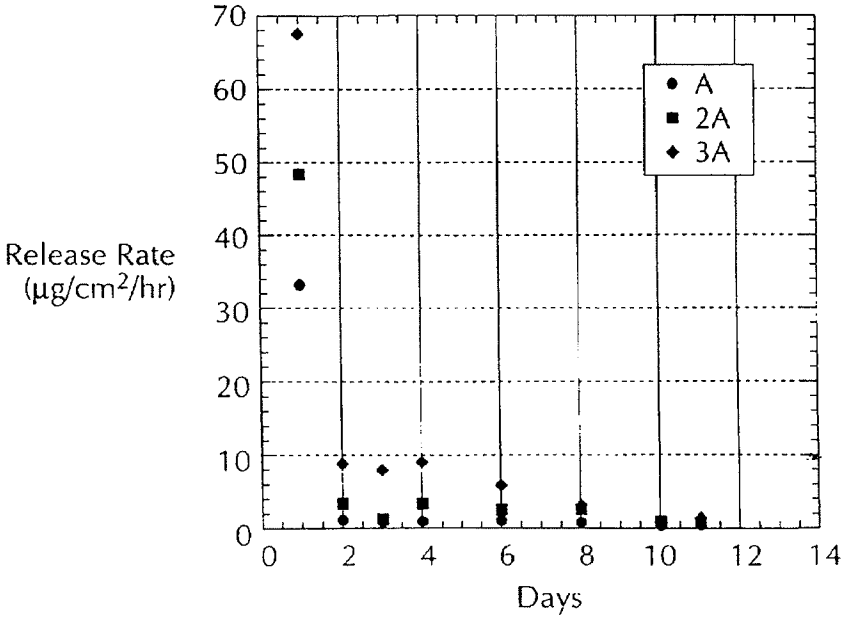
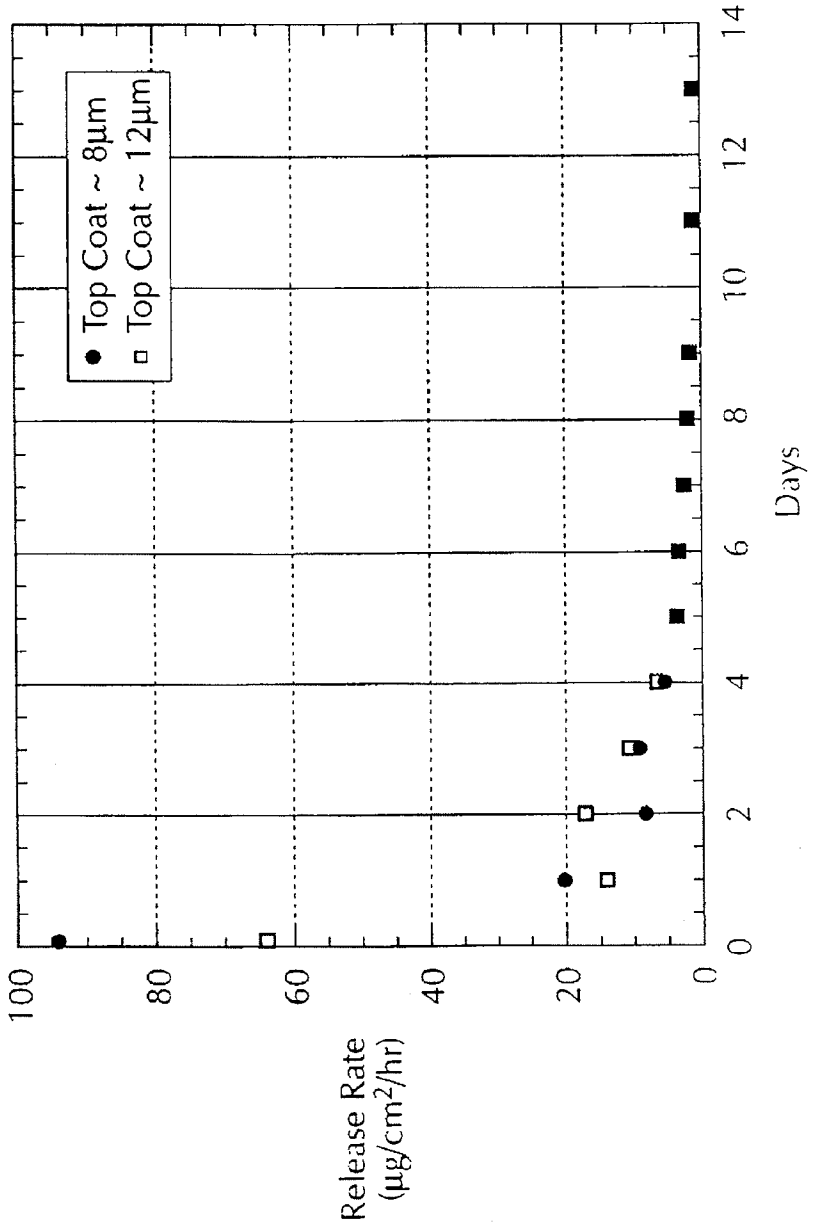

Release Rate (µg/cm²/hr)
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
Days
A
2A
3A

FIG. 6


Top Coat ~ 8µm
Top Coat ~ 12µm
Release Rate (µg/cm²/hr)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Days

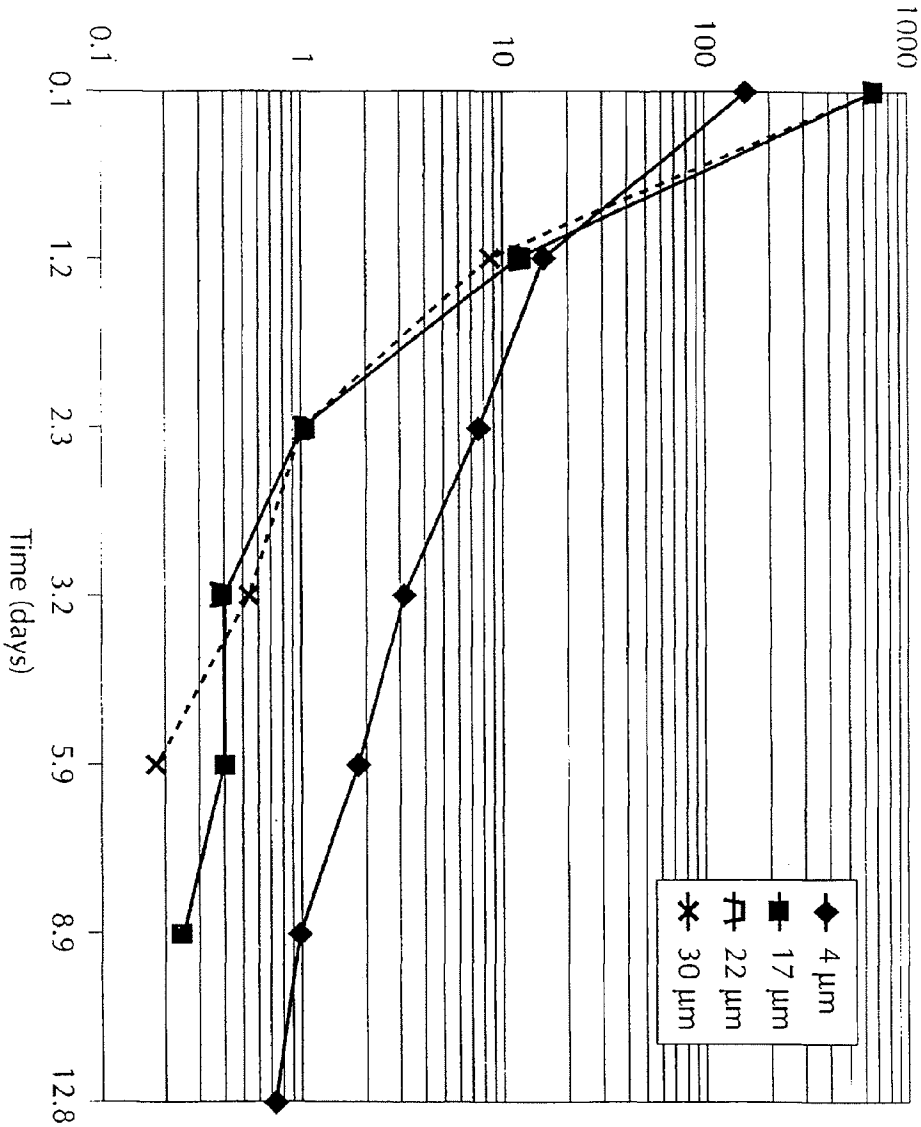

Rate
(µg/cm²/hr)
0.1
1
10
100
1000
Time (days)
0.1
1.2
2.3
3.2
5.9
8.9
12.8
4 µm
17 µm
22 µm
30 µm

FIG. 7

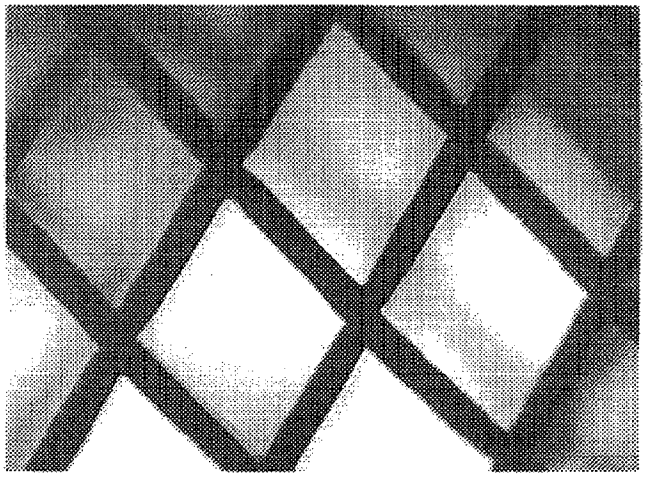


FIG.8

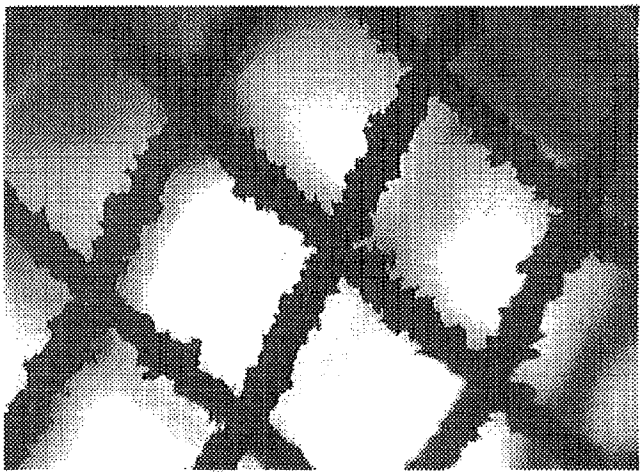


FIG.9

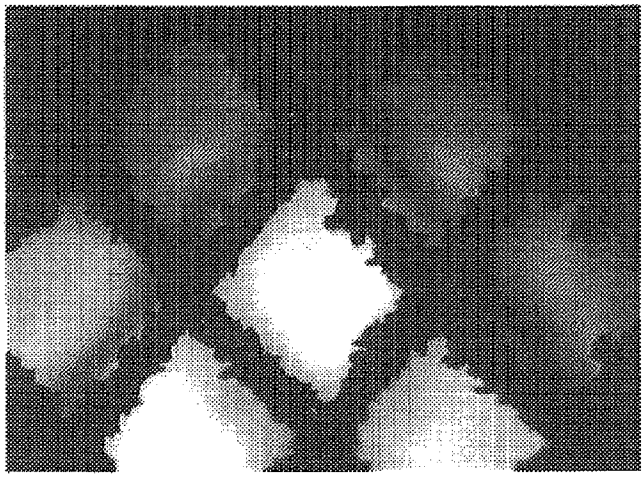


FIG. 10

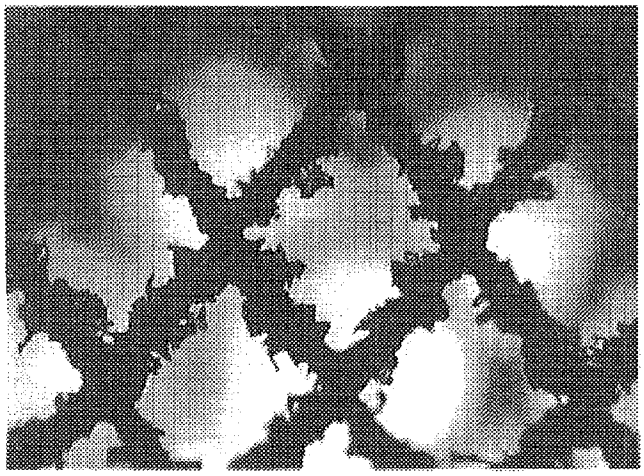


FIG. 11

DRUG RELEASE STENT COATING PROCESS

BACKGROUND OF THE INVENTION

I. Cross-Reference to Related Applications

The present application is a Continuation-In-Part of copending application Ser. No. 08/526,273, abandoned, filed Sep. 11, 1995, and a Continuation-In-Part of copending application Ser. No. 08/424,884, abandoned filed Apr. 19, 1995, all portions of the parent applications not contained in this application being deemed incorporated by reference for any purpose. Cross-reference is also made to application Ser. No. 08/663,518, entitled "DRUG RELEASE STENT COATING AND PROCESS", filed of even date and of common inventorship and assignee, that is also a Continuation-In-Part of both above-referenced patent applications. Any portion of that application that is not contained herein is also deemed to be incorporated by reference for any purpose.

II. Field of the Invention

The present invention relates generally to therapeutic expandable stent prosthesis for implantation in body lumens, e.g., vascular implantation and, more particularly, to a process for providing biostable elastomeric coatings on such stents which incorporate biologically active species having controlled release characteristics directly in the coating structure.

II. Related Art

In surgical or other related invasive medicinal procedures, the insertion and expansion of stent devices in blood vessels, urinary tracts or other difficult to access places for the purpose of preventing restenosis, providing vessel or lumen wall support or reinforcement and for other therapeutic or restorative functions has become a common form of long-term treatment. Typically, such prosthesis are applied to a location of interest utilizing a vascular catheter, or similar transluminal device, to carry the stent to the location of interest where it is thereafter released to expand or be expanded in situ. These devices are generally designed as permanent implants which may become incorporated in the vascular or other tissue which they contact at implantation.

One type of self-expanding stent has a flexible tubular body formed of several individual flexible thread elements each of which extends in a helix configuration with the centerline of the body serving as a common axis. The elements are wound in a common direction, but are displaced axially relative to each other and meet, under crossing a like number of elements also so axially displaced, but having the opposite direction of winding. This configuration provides a resilient braided tubular structure which assumes stable dimensions upon relaxation. Axial tension produces elongation and corresponding diameter contraction that allows the stent to be mounted on a catheter device and conveyed through the vascular system as a narrow elongated device. Once tension is relaxed in situ, the device at least substantially reverts to its original shape. Prosthesis of the class including a braided flexible tubular body are illustrated and described in U.S. Pat. Nos. 4,655,771 and 4,954,126 to Wallsten and 5,061,275 to Wallsten et al.

Implanted stents have also been used to carry medicinal agents, such as thrombolytic agents. U.S. Pat. No. 5,163,952 to Froix discloses a thermal memoried expanding plastic stent device which can be formulated to carry a medicinal agent by utilizing the material of the stent itself as an inert polymeric drug carrier. Pinchuk, in U.S. Pat. No. 5,092,877, discloses a stent of a polymeric material which may be employed with a coating associated with the delivery of drugs. Other patents which are directed to devices of the class utilizing bio-degradable or bio-sorbable polymers include Tang et al, U.S. Pat. No. 4,916,193, and MacGregor, U.S. Pat. No. 4,994,071. Sahatjian in U.S. Pat. No. 5,304,121, discloses a coating applied to a stent consisting of a hydrogel polymer and a preselected drug; possible drugs include cell growth inhibitors and heparin. A further method of making a coated intravascular stent carrying a therapeutic material in which a polymer coating is dissolved in a solvent and the therapeutic material dispersed in the solvent and the solvent thereafter evaporated is described in Berg et al, U.S. Pat. No. 5,464,650, issued Nov. 5, 1995 and corresponding to European patent application 0 623 354 A1 published 09 Nov. 1994.

An article by Michael N. Helmus (a co-inventor of the present invention) entitled "Medical Device Design—A Systems Approach Central Venous Catheters", 22nd International Society for the Advancement of Material and Process Engineering Technical Conference (1990) relates to polymer/drug/membrane systems for releasing heparin. Those polymer/ drug/membrane systems require two distinct layers to function.

The above cross-referenced grandparent application supplies an approach that provides long-term drug release, i.e., over a period of days or even months, incorporated in a controlled-release system. The parent application and present invention provide a process for coating such stents including techniques that enable the initial burst effect of drug elation to be controlled and the drug release kinetic profile associated with long-term therapeutic effect to be modified.

Metal stents of like thickness and weave generally have better mechanical properties than polymeric stents. Metallic vascular stents braided of even relatively fine metal filament can provide a large amount of strength to resist inwardly directed circumferential pressure in blood vessels. In order for a polymer material to provide comparable strength characteristics, a much thicker-walled structure or heavier, denser filament weave is required. This, in turn, reduces the cross-sectional area available for flow through the stent and/or reduces the relative amount of open space available in the structure. In addition, when applicable, it is usually more difficult to load and deliver polymeric stents using vascular catheter delivery systems.

It will be noted, however, that while certain types of stents such as braided metal stents may be superior to others for some applications, the process of the present invention is not limited in that respect and may be used to coat a wide variety of devices. The present invention also applies, for example, to the class of stents that are not self-expanding including those which can be expanded, for instance, with a balloon. Polymeric stents, of all kinds can be coated using the process. Thus, regardless of particular detailed embodiments the use of the invention is not considered or intended to be limited with respect either to stent design or materials of construction. Further, the present invention may be utilized with other types of implant prostheses.

Accordingly, it is a primary object of the present invention to provide a coating process for coating a stent to be used as a deployed stent prosthesis, the coating being capable of long-term delivery of biologically active materials.

Another object of the invention is to provide a process for coating a stent prosthesis using a biostable hydrophobic elastomer in which biologically active species are incorporated within a cured coating.

Still another object of the present invention is to provide a multi-layer coating in which the percentage of active material can vary from layer to layer.

A further object of the present invention is to control or modify aspects of the timed or time variable drug delivery from a stent coating by controlling average particle size in the biologically active species.

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

SUMMARY OF THE INVENTION

The present invention provides processes for producing a relatively thin layer of biostable elastomeric material in which an amount of biologically active material is dispersed as a coating on the surfaces of a deployable stent prosthesis. The preferred stent to be coated is a self-expanding, open-ended tubular stent prosthesis. Although other materials, including polymer materials, can be used, in the preferred embodiment, the tubular body is formed of an open braid of fine single or polyfilament metal wire which flexes without collapsing and readily axially deforms to an elongate shape for transluminal insertion via a vascular catheter. The stent resiliently attempts to resume predetermined stable dimensions upon relaxation in situ.

The coating is preferably applied as a mixture, solution or suspension of polymeric material and finely divided biologically active species dispersed in an organic vehicle or a solution or partial solution of such species in a solvent or vehicle for the polymer and/or biologically active species. For the purpose of this application, the term "finely divided" means any type or size of included material from dissolved molecules through suspensions, colloids and particulate mixtures. The active material is dispersed in a carrier material which may be the polymer, a solvent, or both. The coating is preferably applied as a plurality of relatively thin layers sequentially applied in relatively rapid sequence and is preferably applied with the stent in a radially expanded state. In some applications the coating may further be characterized as a composite initial tie coat or undercoat and a composite topcoat. The coating thickness ratio of the topcoat to the undercoat may vary with the desired effect and/or the elution system. Typically these are of different formulations.

The coating may be applied by dipping or spraying using evaporative solvent materials of relatively high vapor pressure to produce the desired viscosity and quickly establish coating layer thicknesses. The preferred process is predicated on reciprocally spray coating a rotating radially expanded stent employing an air brush device. The coating process enables the material to adherently conform to and cover the entire surface of the filaments of the open structure of the stent but in a manner such that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The coating is exposed to room temperature ventilation for a predetermined time (possibly one hour or more) for solvent vehicle evaporation. Thereafter the polymeric precuser material is cured at room temperature or elevated temperatures or the solvent evaporated away from the dissolved polymer as the case may be curing is defined as the process of converting the elastomeric or polymeric material into the finished or useful state by the application of heat and/or chemical agents which include physical-chemical charges. Where, for example, polyurethane thermoplastic elastomers are used, solvent evaporation can occur at room temperature rendering the polymeric material useful for controlled drug release without further curing. Non-limiting examples of curing according to this definition include the application of heat and/or chemical agents and the evaporation of solvent which may induce physical and/or chemical changes.

The ventilation time and temperature for cure are determined by the particular polymer involved and particular drugs used. For example, silicone or polysiloxane materials (such as polydimethylsiloxane) have been used successfully. These materials are applied as pre-polymer in the coating composition and must thereafter be cured. The preferred species have a relatively low cure temperatures and are known as a room temperature vulcanizable (RTV) materials. Some polydimethylsiloxane materials can be cured, for example, by exposure to air at about 90° C. for a period of time such as 16 hours. A curing step may be implemented both after application of a certain number of lower undercoat layers and the topcoat layers or a single curing step used after coating is completed.

The coated stents may thereafter be subjected to a post-cure sterilization process which includes an inert gas plasma treatment, and then exposure to gamma radiation, electron beam, ethylene oxide (ETO) or steam sterilization may also be employed.

In the plasma treatment, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to about 20–50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150–650 standard ml per minute, which is equivalent to about 100–450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After the argon plasma pretreatment, the coated and cured stents are subjected to gamma radiation sterilization nominally at 2.5–3.5 Mrad. The stents enjoy full resiliency after radiation whether exposed in a constrained or non-constrained status. It has been found that constrained stents subjected to gamma sterilization without utilizing the argon plasma pretreatment lose resiliency and do not recover at a sufficient or appropriate rate.

The elastomeric material that forms a major constituent of the stent coating should possess certain properties. It is preferably a suitable hydrophobic biostable elastomeric material which does not degrade and which minimizes tissue rejection and tissue inflammation and one which will undergo encapsulation by tissue adjacent to the stent implantation site. Polymers suitable for such coatings include silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes (including polycarbonate urethanes), thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM (ethylene-propylene terpolymer) rubbers and polyamide elastomers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention.

Agents suitable for incorporation include antithrobotics, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, antinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, antibiotics growth factors, growth factor

inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive action may come from inhibiting particular cells (e.g., smooth muscle cells) or tissue formation (e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

The preferred materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemoried alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as ELGILOY® and PHYNOX. Further details concerning the fabrication and details of other aspects of the stents themselves, may be gleaned from the above referenced U.S. Pat. Nos. 4,655,771 and 4,954,126 to Wallsten and 5,061,275 to Wallsten et al. To the extent additional information contained in the above-referenced patents is necessary for an understanding of the present invention, they are deemed incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating, and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

For the purposes of this specification, "elution" is defined as any process of release that involves extraction or release by direct contact of the material with bodily fluids through the interparticle paths connected with the exterior of the coating. "Transport" or "diffusion" are defined to include a mechanism of release in which a material released traverses through another material.

The desired release rate profile can be tailored by varying the coating thickness, the radial distribution (layer to layer) of bioactive materials, the mixing method, the amount of bioactive material, the combination of different matrix polymer materials at different layers, and the crosslink density of the polymeric material. The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, during the curing process, determines the amount of crosslinking and so the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as heparin, a crosslink structure of greater density will increase release time and reduce burst effect.

Additionally, with eluting materials such as heparin, release kinetics, particularly initial drug release rate, can be affected by varying the average dispersed particle size. The observed initial release rate or burst effect may be substantially reduced by using smaller particles, particularly if the particle size is controlled to be less than about 15 microns and the effect is even more significant in the particle size range of $\leqq$10 microns, especially when the coating thickness is not more than about 50 μm and drug loading is about 25–45 weight percent.

It will also be appreciated that an unmedicated silicone thin top layer provides an advantage over drug containing top coat. Its surface has a limited porosity and is generally smooth, which may be less thrombogeneous and may reduce the chance to develop calcification, which occurs most often on the porous surface.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate like parts throughout the same:

FIG. **1** is a schematic flow diagram illustrating the steps of the process of the invention;

FIG. **2** represents a release profile for a multi-layer system showing the percentage of heparin released over a two-week period;

FIG. **3** represents a release profile for a multi-layer system showing the relative release rate of heparin over a two-week period;

FIG. **4** illustrates a profile of release kinetics for different drug loadings at similar coating thicknesses illustrating the release of heparin over a two-week period;

FIG. **5** illustrates drug elution kinetics at a given loading of heparin over a two-week period at different coating thicknesses;

FIG. **6** illustrates the release kinetics in a coating having a given tie-layer thickness for different top coat thicknesses in which the percentage heparin in the tie coat and top coats are kept constant;

FIG. **7** illustrates the release kinetics of several coatings having an average coating thickness of 25 microns and a heparin loading of 37.5% but using four different average particle sizes;

FIGS. **8–11** are photomicrographs of coated stent fragments for the coatings of FIG. **7** having a corresponding average particle size of 4 microns, 17 microns, 22 microns and 30 microns, respectively.

DETAILED DESCRIPTION

According to the present invention, the stent coatings incorporating biologically active materials for timed delivery in situ in a body lumen of interest are preferably sprayed in many thin layers from prepared coating solutions or suspensions. The steps of the process are illustrated generally in FIG. **1**. The coating solutions or suspensions are prepared at 10 as will be described later. The desired amount of crosslinking agent is added to the suspension/solution as at 12 and material is then agitated or stirred to produce a homogenous coating composition at 14 which is thereafter transferred to an application container or device which may be a container for spray painting at 16. Typical exemplary preparations of coating solutions that were used for heparin and dexamethasone appear next.

General Preparation of Heparin Coating Composition

Silicone was obtained as a polymer precursor in solvent (xylene) mixture. For example, a 35% solid silicone weight content in xylene was procured from Applied Silicone, Part #40,000. First, the silicone-xylene mixture was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated amounts of finely divided heparin (2–6 microns) were added into the silicone, then tetrahydrofuron (THF) HPCL grade (Aldrich or EM) was added. For a 37.5% heparin coating, for example: $W_{silicone}$=5 g; solid percent =35%; W_{hep}=5×0.35×0.375/(0.625)=1.05 g. The amount of THF needed (44 ml) in the coating solution was calculated by using the equation $W_{silicone\ solid}/V_{THF}$=0.04 for a 37.5% heparin coating solution). Finally, the manufacturer crosslinker solution was added by using Pasteur P-pipet. The amount of crosslinker

added was formed to effect the release rate profile. Typically, five drops of crosslinker solution were added for each five grams of silicone-xylene mixture. The crosslinker may be any suitable and compatible agent including platinum and peroxide based materials. The solution was stirred by using the stirring rod until the suspension was homogenous and milk-like. The coating solution was then transferred into a paint jar in condition for application by air brush.

General Preparation of Dexamethasone Coating Composition

Silicone (35% solution as above) was weighed into a beaker on a Metler balance. The weight of dexamethasone free alcohol or acetate form was calculated by silicone weight multiplied by 0.35 and the desired percentage of dexamethasone (1 to 40%) and the required amount was then weighed. Example: $W_{silicone}$=5 g; for a 10% dexamethasone coating, W_{dex}=5×0.35×0.1/0.9=0.194 g and THF needed in the coating solution calculated. $W_{silicone\ solid}/V_{THF}$=0.06 for a 10% dexamethasone coating solution. Example: $W_{silicone}$=5 g; V_{THF}=5×0.35/0.06 ≈29 ml. The dexamethasone was weighed in a beaker on an analytical balance and half the total amount of THF was added. The solution was stirred well to ensure full dissolution of the dexamethasone. The stirred DEX-THF solution was then transferred to the silicone container. The beaker was washed with the remaining THF and this was transferred to the silicone container. The crosslinker was added by using a Pasteur pipet. Typically, five drops of crosslinker were used for five grams of silicone.

The application of the coating material to the stent was quite similar for all of the materials and the same for the heparin and dexamethasone suspensions prepared as in the above Examples. The suspension to be applied was transferred to an application device, typically a paint jar attached to an air brush, such as a Badger Model 150, supplied with a source of pressurized air through a regulator (Norgren, 0–160 psi). Once the brush hose was attached to the source of compressed air downstream of the regulator, the air was applied. The pressure was adjusted to approximately 15–25 psi and the nozzle condition checked by depressing the trigger.

Any appropriate method can be used to secure the stent for spraying and rotating fixtures were utilized successfully in the laboratory. Both ends of the relaxed stent were fastened to the fixture by two resilient retainers, commonly alligator clips, with the distance between the clips adjusted so that the stent remained in a relaxed, unstretched condition. The rotor was then energized and the spin speed adjusted to the desired coating speed, nominally about 40 rpm.

With the stent rotating in a substantially horizontal plane, the spray nozzle was adjusted so that the distance from the nozzle to the stent was about 2–4 inches and the composition was sprayed substantially horizontally with the brush being directed along the stent from the distal end of the stent to the proximal end and then from the proximal end to the distal end in a sweeping motion at a speed such that one spray cycle occurred in about three stent rotations. Typically a pause of less than one minute, normally about one-half minute, elapsed between layers. Of course, the number of coating Layers did and will vary with the particular application. For example, for a coating level of 3–4 mg of heparin per cm^2 of projected area, 20 cycles of coating application are required and about 30 ml of solution will be consumed for a 3.5 mm diameter by 14.5 cm long stent.

The rotation speed of the motor, of course, can be adjusted as can the viscosity of the composition and the flow rate of the spray nozzle as desired to modify the layered structure. Generally, with the above mixes, the best results have been obtained at rotational speeds in the range of 30–50 rpm and with a spray nozzle flow rate in the range of 4–10 ml of coating composition per minute, depending on the stent size. It is contemplated that a more sophisticated, computer-controlled coating apparatus will successfully automate the process demonstrated as feasible in the laboratory.

Several applied layers make up what is called the tie layer as at **18** and thereafter additional upper layers, which may be of a different composition with respect to bioactive material, the matrix polymeric materials and crosslinking agent, for example, are applied as the top layer as at **20**. The application of the top layer follows the same coating procedure as the tie layer with the number and thickness of layers being optional. Of course, the thickness of any layer can be adjusted by modifying the speed of rotation of the stent and the spraying conditions. Generally, the total coating thickness is controlled by the number of spraying cycles or thin coats which make up the total coat.

As shown at **22** in FIG. **1**, the coated stent is thereafter subjected to a curing step in which the pre-polymer and crosslinking agents cooperate to produce a cured polymer matrix containing the biologically active species. The curing process involves evaporation of the solvent xylene, THF, etc. and the curing and crosslinking of the polymer. Certain silicone materials can be cured at relatively low temperatures, (i.e. RT-50° C.) in what is known as a room temperature vulcanization (RTV) process. More typically, however, the curing process involves higher temperature curing materials and the coated stents are put into an oven at approximately 90° C. or higher for approximately 16 hours. The temperature may be raised to as high as 150° C. for dexamethasone containing coated stents. Of course, the time and temperature may vary with particular silicones, crosslinkers, and biologically active species.

Stents coated and cured in the manner described need to be sterilized prior to packaging for future implantation. For sterilization, gamma radiation is a preferred method particularly for heparin containing coatings; however, it has been found that stents coated and cured according to the process of the invention subjected to gamma sterilization may be too slow to recover their original posture when delivered to a vascular or other lumen site using a catheter unless a pretreatment step as at **24** is first applied to the coated, cured stent.

The pretreatment step involves an argon plasma treatment of the coated, cured stents in the unconstrained configuration. In accordance with this procedure, the stents are placed in a chamber of a plasma surface treatment system such as a Plasma Science 350 (Himont/Plasma Science, Foster City, Calif.). The system is equipped with a reactor chamber and RF solid-state generator operating at 13.56 mHz and from 0–500 watts power output and being equipped with a microprocessor controlled system and a complete vacuum pump package. The reaction chamber contains an unimpeded work volume of 16.75 inches (42.55 cm) by 13.5 inches (34.3 cm) by 17.5 inches (44.45 cm) in depth.

In the plasma process, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20–50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150–650 standard ml per minute, which is equivalent to

100–450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After this, as shown at **26**, the stents are exposed to gamma sterilization at 2.5–3.5 Mrad. The radiation may be carried out with the stent in either the radially non-constrained status—or in the radially constrained status.

With respect to the anticoagulant material heparin, the percentage in the tie layer is nominally from about 20–50% and that of the top layer from about 0–30% active material. The coating thickness ratio of the top layer to the tie layer varies from about 1:10 to 1:2 and is preferably in the range of from about 1:6 to 1:3.

Suppressing the burst effect also enables a reduction in the drug loading or in other words, allows a reduction in the coating thickness, since the physician will give a bolus injection of antiplatelet/anticoagulation drugs to the patient during the stenting process. As a result, the drug imbedded in the stent can be fully used without waste. Tailoring the first day release, but maximizing second day and third day release at the thinnest possible coating configuration will reduce the acute or subcute thrombosis.

FIG. **4** depicts the general effect of drug loading for coatings of similar thickness. The initial elution rate increases with the drug loading as shown in FIG. **5**. The release rate also increases with the thickness of the coating at the same loading but tends to be inversely proportional to the thickness of the top layer as shown by the same drug loading and similar tie-coat thickness in FIG. **6**.

The effect of average particle size is depicted in the FIGS. **7–11** in which coating layers with an average coating thickness of about 25 microns (μm), prepared and sterilized as above, were provided with dispersed heparin particles (to 37.5% heparin) of several different average particle sizes. FIG. **7** shows plots of elution kinetics for four different sizes of embedded heparin particles. The release took place in phosphate buffer (pH 7.4) at 37° C. The release rate using smaller, particularly 4–6μm average sized particles noticeably reduces the initial rate or burst effect and thereafter the elution rate decreases more slowly with time. Average particle sizes above about 15 μm result in initial release rates approaching bolus elution. This, of course, is less desirable, both from the standpoint of being an unnecessary initial excess and for prematurely depleting the coating of deserved drug material.

In addition, as shown in the photomicrographs of FIGS. **8–11**, as the average particle size increases, the morphology of the coating surface also changes. Coatings containing larger particles (FIGS. **9–11**) have very rough and irregular surface characteristics. These surface irregularities may be more thrombogenic or exhibit an increased tendency to cause embolization when the corresponding stent is implanted in a blood vessel.

Accordingly, it has been found that the average particle size should generally be controlled below about 15 μm to reduce the burst effect and preferably should be $\leq$about 10 μm for best results. The 4–6 μm size worked quite successfully in the laboratory. However, it should be noted that larger particle size can also be advantageously used, for instance, when the drug load is low, such as below 25 weight percent. Elution kinetics can be adjusted by a combination of changing the particle size and changing the load or concentration of the dispersed drug material.

What is apparent from the data gathered to date, however, is that the process of the present invention enables the drug elution kinetics to be modified to meet the needs of the particular stent application. In a similar manner, stent coatings can be prepared using a combination of two or more drugs and the drug release sequence and rate controlled. For example, antiproliferation drugs may be combined in the undercoat and anti-thrombotic drugs in the topcoat layer. In this manner, the anti-thrombotic drugs, for example, heparin, will elute first followed by antiproliferation drugs, e.g. dexamethasone, to better enable safe encapsulation of the implanted stent.

The heparin concentration measurement were made utilizing a standard curve prepared by complexing azure A dye with dilute solutions of heparin. Sixteen standards were used to compile the standard curve in a well-known manner.

For the elution test, the stents were immersed in a phosphate buffer solution at pH 7.4 in an incubator at approximately 37° C. Periodic samplings of the solution were processed to determine the amount of heparin eluted. After each sampling, each stent was placed in heparin-free buffer solution.

As stated above, while the allowable loading of the elastomeric material with heparin may vary, in the case of silicone materials heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In the case of dexamethasone, the loading may be as high as 50% or more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a thin surface coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

Whereas the above examples depict coatings having two different drug loadings or percentages of biologically active material to be released, this is by no means limiting with respect to the invention and it is contemplated that any number of layers and combinations of loadings can be employed to achieve a desired release profile. For example, gradual grading and change in the loading of the layers can be utilized in which, for example, higher loadings are used in the inner layers. Also layers can be used which have no drug loadings at all. For example, a pulsatile heparin release system may be achieved by a coating in which alternate layers containing heparin are sandwiched between unloaded layers of silicone or other materials for a portion of the coating. In other words, the invention allows untold numbers of combinations which result in a great deal of flexibility with respect to controlling the release of biologically active materials with regard to an implanted stent. Each applied layer is typically from approximately 0.5 microns to 15

microns in thickness. The total number of sprayed layers, of course, can vary widely, from less than 10 to more than 50 layers; commonly, 20 to 40 layers are included. The total thickness; of the coating can also vary widely, but can generally be from about 10 to 200 microns.

Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials include silicone rubber elastomers and biostable polyurethanes specifically.

This invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use embodiments of the example as required. However, it is to be understood that the invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

We claim:

1. A method of coating at least a portion of an implantable prosthesis, having at least one opening therein, with a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom comprising the steps of:

(a) applying a coating comprising the elastomeric material, a solvent and an amount of finely divided biologically active material onto at least a portion of the prosthesis; wherein when the biologically active material is particulate the average particle size of the biologically active material is less than or equal to about 15 μm; and wherein the coating is applied to the prosthesis in a manner to adheringly conform thereto to preserve the opening; and

(b) curing the coating such that at least some of the biologically active material is particulate after curing.

2. The method of claim 1 wherein the elastomeric material is selected from the group consisting of silicones, polyurethanes, polyamide elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, ethylene-propylene terpolymer rubbers and combinations thereof.

3. The method of claim 1 wherein the biologically active material includes heparin.

4. The method of claim 1 wherein the coating comprises about 25–45 weight percent biologically active material.

5. The method of claim 1 wherein the biologically active material has an average particle size less than or equal to about 10 μm before curing.

6. The method of claim 5 wherein the biologically active material includes heparin.

7. A method of controlling the delivery of an eluting material incorporated in an elastomeric coating having at least one layer on at least a portion of an implantable prosthesis having at least one opening therein, the method comprising incorporating a biologically active particulate material having an average particle size of less than or equal to about 15 μm into at least one layer of the coating and applying the elastomeric coating in a manner which adheringly conforms to the surface to preserve the opening; and curing the coating such that at least some of the biologically active material is particulate after curing.

8. The method of claim 7 wherein said biologically active material is heparin.

9. The method of claim 7 wherein the layer comprises about 25–45 weight percent biologically active material.

10. The method of claim 7 wherein the biologically active material is incorporated to produce a substantially smooth surface on the prosthesis.

11. The method of claim 1 wherein the elastomeric material, solvent and biologically active material are applied by spraycoating the prosthesis.

12. The method of claim 1 wherein the elastomeric material, solvent and biologically active material are applied by dipping the prosthesis.

13. The method of claim 7 wherein the biologically active material has an average particle size less than or equal to about 10 μm before curing.

14. The method of claim 1 wherein the implantable prosthesis is an expandable stent having a tubular metal body having open ends and a sidewall structure having openings therein, and wherein the elastomeric material, solvent and biologically active material form a coating on a surface of said sidewall structure which continuously conforms to said sidewall structure in a manner that preserves the openings when the stent is expanded.

15. The method of claim 13 wherein the elastomeric material, solvent and biologically active material are applied with the stent fully expanded.

16. The method of claim 1 wherein the elastomeric material, solvent and biologically active material are in a mixture.

17. The method of claim 1 wherein the biologically active material has an average particle size of less than or equal to about 15 μm after curing.

18. The method of claim 5 wherein the biologically active material has an average particle size of less than or equal to about 15 μm after curing.

* * * * *

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United States Patent [19]

Ding et al.

[11] Patent Number: 6,120,536

[45] Date of Patent: *Sep. 19, 2000

[54] **MEDICAL DEVICES WITH LONG TERM NON-THROMBOGENIC COATINGS**

[75] Inventors: **Ni Ding**, Plymouth, Minn.; **Michael N. Helmus**, Long Beach, Calif.

[73] Assignee: **Schneider (USA) Inc.**, Minneapolis, Minn.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **08/663,518**

[22] Filed: **Jun. 13, 1996**

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/526,273, Sep. 11, 1995, abandoned, and a continuation-in-part of application No. 08/424,884, Apr. 19, 1995, abandoned.

[51] **Int. Cl.**[7] **A61F 2/06**

[52] **U.S. Cl.** **623/1.43**; 623/1.18; 623/1.46; 424/424; 427/2.21; 427/2.24

[58] **Field of Search** 623/1, 11, 12, 623/1.15, 1.18, 1.42, 1.43, 1.44, 1.45, 1.46; 606/191, 194, 195; 604/890.1, 891.1; 424/422, 423, 424; 427/2.1, 2.12, 2.24, 2.21

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Assistant Examiner—Tram A. Nguyen

[57] **ABSTRACT**

A coating and method for implantable open lattice metallic stent prostheses are disclosed. The coating includes a relatively thin layer of biostable elastomeric material containing an amount of biologically active material, particularly heparin, dispersed in the coating in combination with a non-thrombogenic surface. In one embodiment, the surface is provided with sites of high electronegativity species by coating with fluorosilicone which aid in controlling elution, particularly the initial release rate, and reduced thrombogenic activity. Other non-thrombogenic outer layers for heparin such as covalently bound polyethylene glycol (PEG) are also disclosed.

12 Claims, 8 Drawing Sheets

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Figure 1

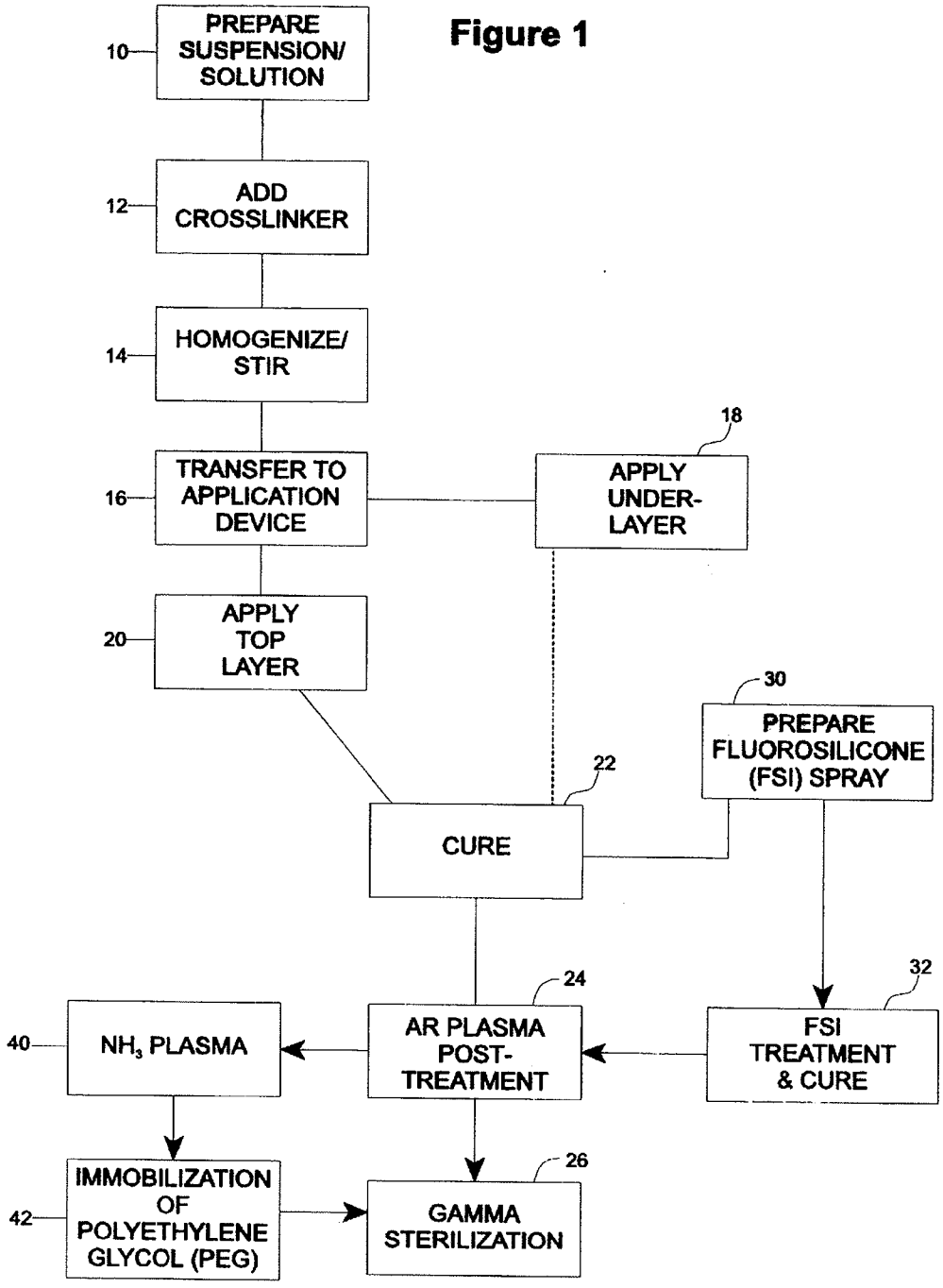
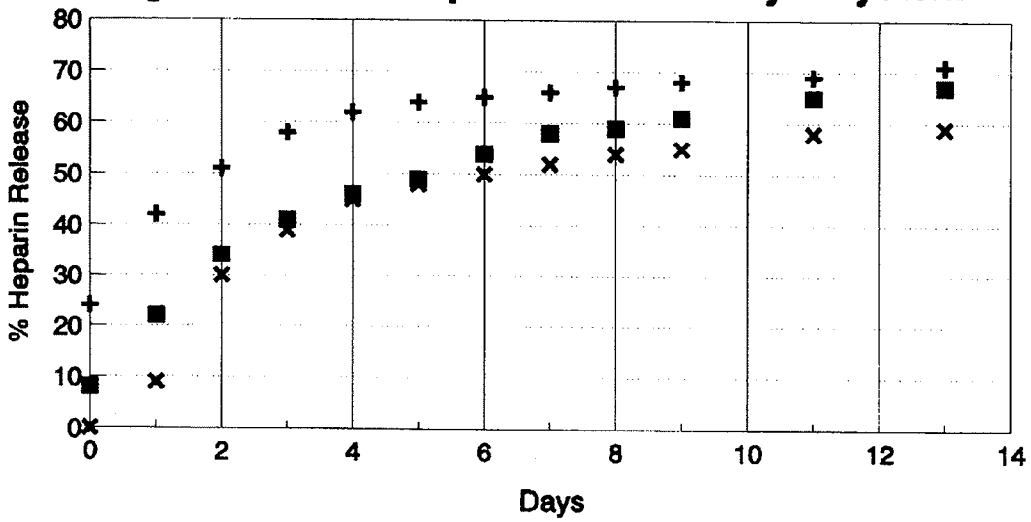

10
PREPARE SUSPENSION/ SOLUTION
12
ADD CROSSLINKER
14
HOMOGENIZE/ STIR
16
TRANSFER TO APPLICATION DEVICE
18
APPLY UNDER-LAYER
20
APPLY TOP LAYER
30
PREPARE FLUOROSILICONE (FSI) SPRAY
22
CURE
24
AR PLASMA POST-TREATMENT
32
FSI TREATMENT & CURE
40
NH3 PLASMA
42
IMMOBILIZATION OF POLYETHYLENE GLYCOL (PEG)
26
GAMMA STERILIZATION

Figure 2. Release profile for multilayer system

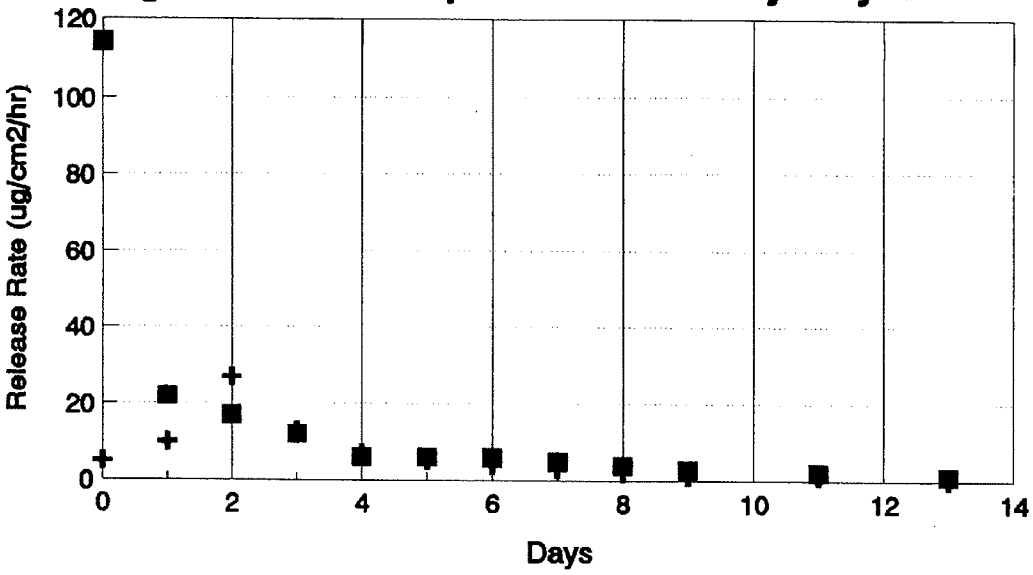


× Tie Layer = 37.5% Hep coating, top layer = silicone

■ Tie Layer = 37.5% Hep coating, top layer = 16.7% Hep coating

\+ Single Layer = 37.5% Hep coating

Figure 3. Release profile for multilayer system



+ Tie Layer = 37.5% Hep coating, top layer = silicone

▪ Tie Layer = 37.5% Hep coating, top layer = 16.7% Hep coating

Figure 4. Release kinetics for different drug loading at the similar coating thickness

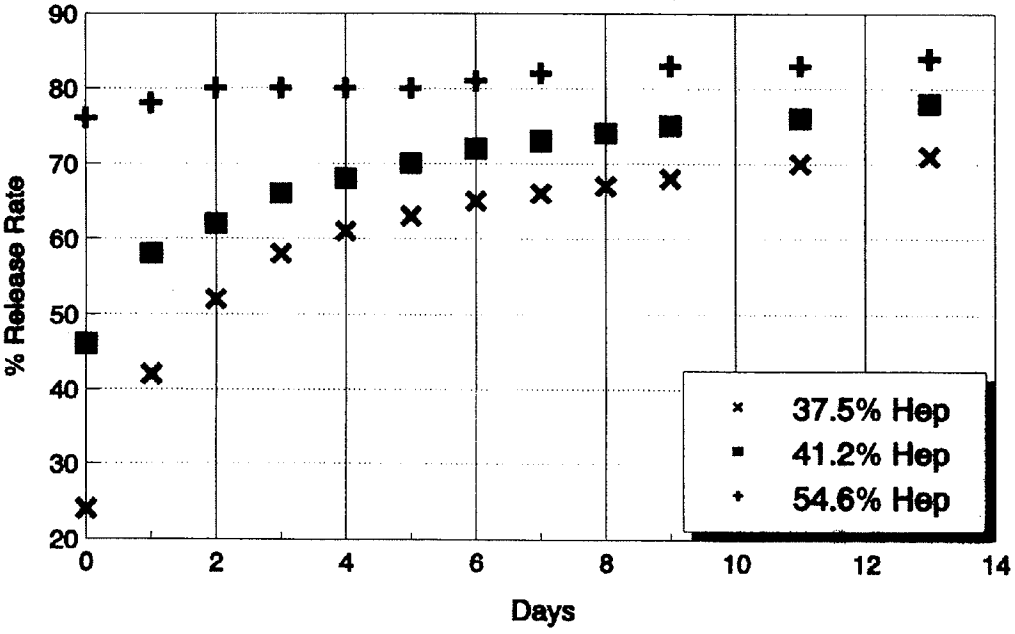


Figure 5. Drug elution kinetics at different coating thickness (A ~ 10-15um). Drug loading = 41.1%

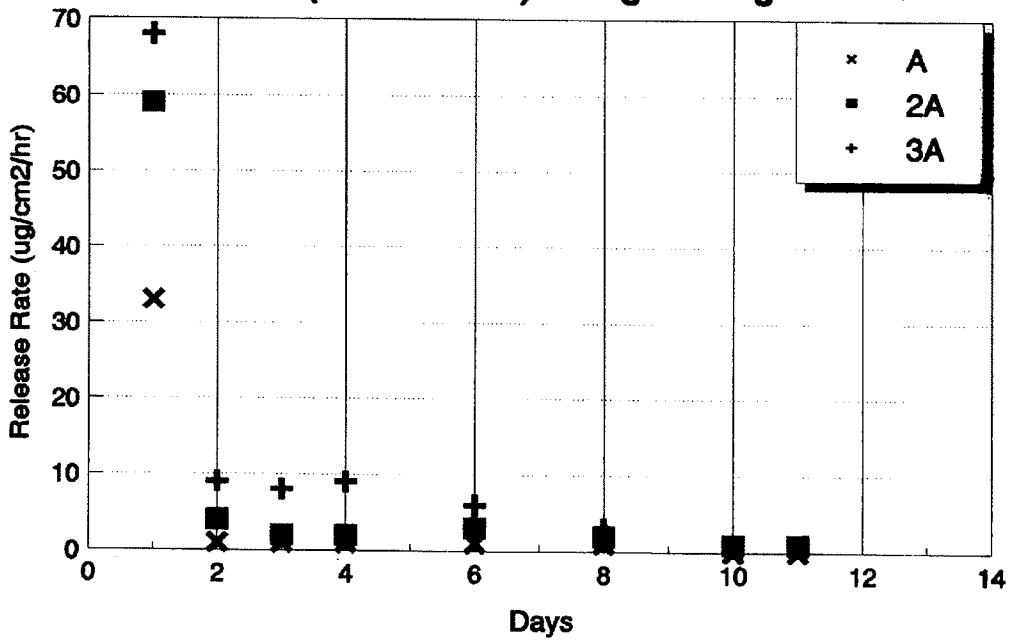


Figure 6. 37.5% Hep in tie-coat with the same tie-coat thickness and 16.7% Hep in top-coat

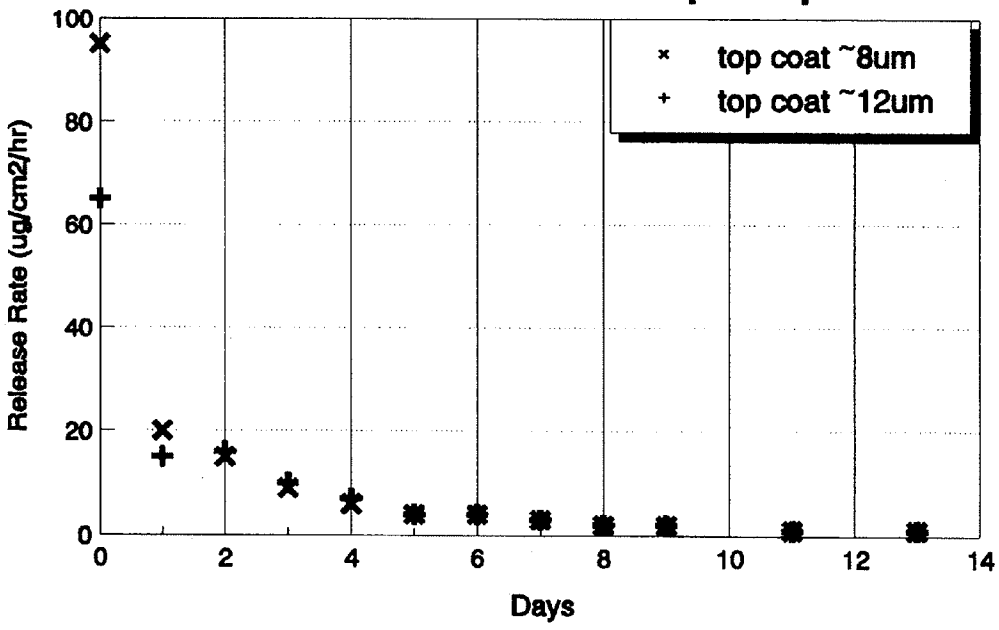


Figure 7. W or w/o fluorosilicone (FSI) top coat

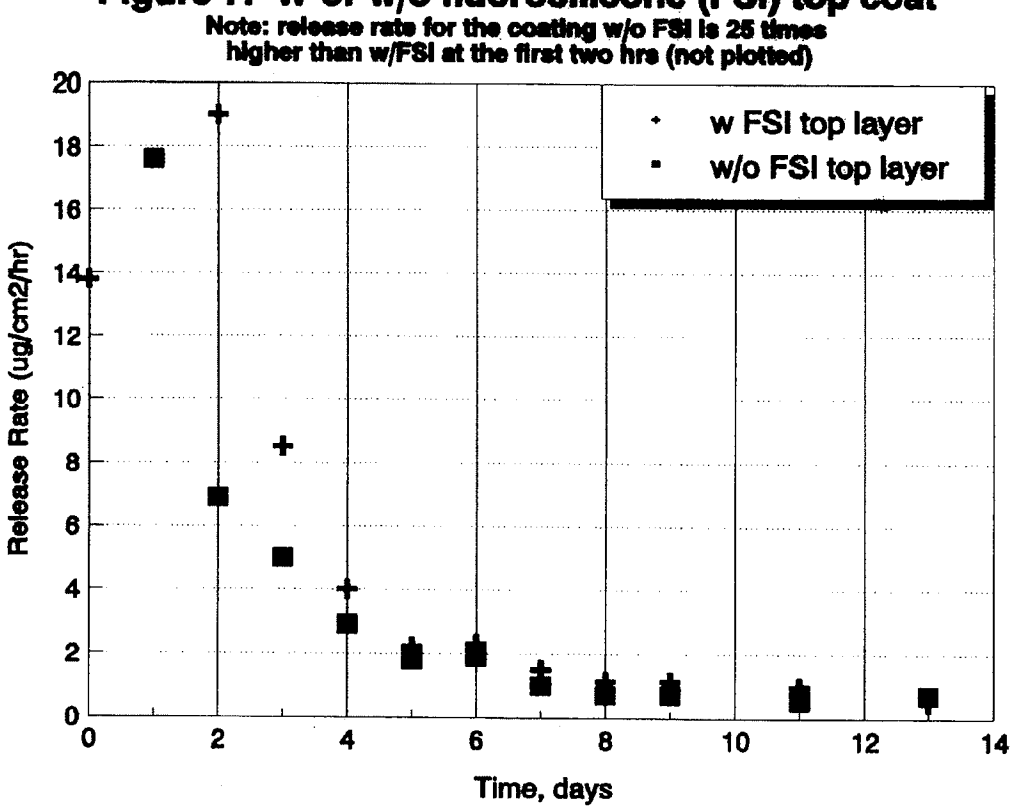
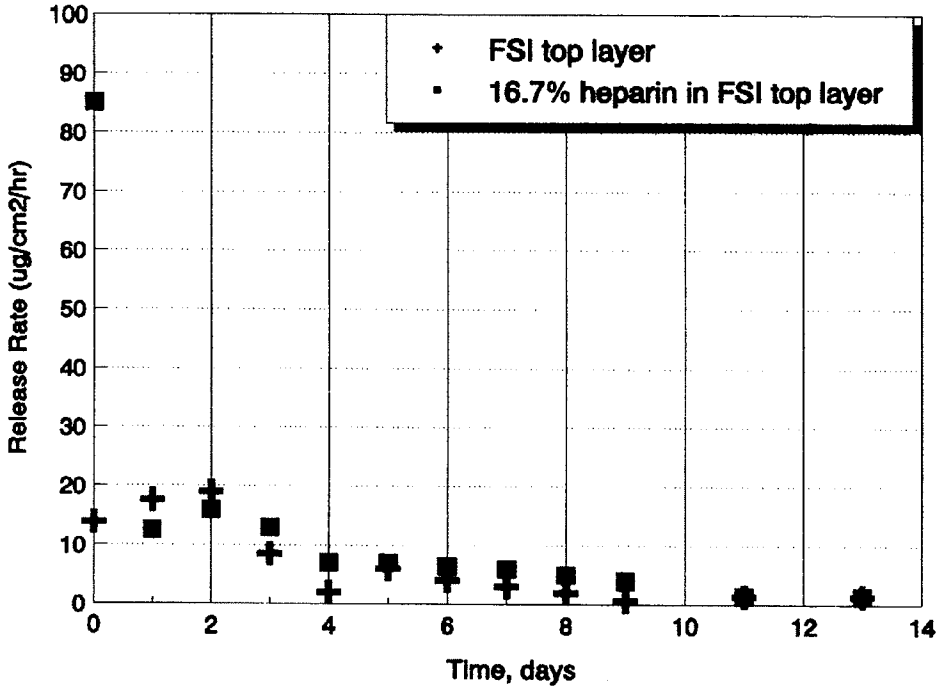


Figure 8. Comparison of fluorosilicone (FSI) top coat w or w/o heparin. The thickness of the tie coat (37.5%) heparin is about 40 micron.



MEDICAL DEVICES WITH LONG TERM NON-THROMBOGENIC COATINGS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a Continuation-In-Part of application Ser. No. 08/526,273, filed Sep. 11, 1995, now abandoned, and a Continuation-In-Part of application Ser. No. 08/424,884, filed Apr. 19, 1995, now abandoned, all portions of the parent applications not contained in this application being deemed incorporated by reference for any purpose. Cross-reference is also made to Ser. No. 08/663,490, entitled "DRUG RELEASE STENT COATING PROCESS, filed of even date, of common inventorship and assignee, now U.S. Pat. No. 5,837,313 and also a Continuation-In-Part of both above-referenced applications. To the extent that it is not contained herein, that application is also deemed incorporated herein by reference for any purpose.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to providing biostable elastomeric coatings on the surfaces of implants which incorporate biologically active species having controlled release characteristics in the coating particularly to providing a non-thrombogenic surface during and after timed release of the biologically active species. The invention is particularly described in terms of coatings on therapeutic expandable stent prostheses for implantation in body lumens, e.g., vascular implantation.

2. Related Art

In surgical or other related invasive procedures, the insertion and expansion of stent devices in blood vessels, urinary tracts or other locations difficult to otherwise access for the purpose of preventing restenosis, providing vessel or lumen wall support or reinforcement and for other therapeutic or restorative functions has become a common form of long-term treatment. Typically, such prostheses are applied to a location of interest utilizing a vascular catheter, or similar transluminal device, to carry the stent to the location of interest where it is thereafter released to expand or be expanded in situ. These devices are generally designed as permanent implants which may become incorporated in the vascular or other tissue which they contact at implantation.

One type of self-expanding stent has a flexible tubular body formed of several individual flexible thread elements each of which extends in a helix configuration with the centerline of the body serving as a common axis. The elements are wound in the same direction but are displaced axially relative to each other and meet, under crossing, a like number of elements also so axially displaced, but having the opposite direction of winding. This configuration provides a resilient braided tubular structure which assumes stable dimensions upon relaxation. Axial tension produces elongation and corresponding diameter contraction that allows the stent to be mounted on a catheter device and conveyed through the vascular system as a narrow elongated device. Once tension is relaxed in situ, the device at least substantially reverts to its original shape. Prostheses of the class including a braided flexible tubular body are illustrated and described in U.S. Pat. Nos. 4,655,771 and 4,954,126 to Wallsten and U.S. Pat. No. 5,061,275 to Wallsten et al.

Implanted stents have been used to carry medicinal agents, such as thrombolytic agents. U.S. Pat. No. 5,163,952 to Froix discloses a thermal memoried expanding plastic stent device formulated to carry a medicinal agent in the material of the stent itself. Pinchuk, in U.S. Pat. No. 5,092,877, discloses a stent of a polymeric material which may have a coating associated with the delivery of drugs. Other patents which are directed to devices of the class utilizing bio-degradable or bio-sorbable polymers include Tang et al, U.S. Pat. No. 4,916,193, and MacGregor, U.S. Pat. No. 4,994,071.

A patent to Sahatjian, U.S. Pat. No. 5,304,121, discloses a coating applied to a stent consisting of a hydrogel polymer and a preselected drug such as cell growth inhibitors or heparin. A further method of making a coated intravascular stent carrying a therapeutic material is described in Berg et al., U.S. Pat. No. 5,464,650, issued on Nov. 7, 1995 and corresponding to European Patent Application No. 0 623 354 A1 published Nov. 9, 1994. In that disclosure, a polymer coating material is dissolved in a solvent and the therapeutic material dispersed in the solvent; the solvent evaporated after application.

An article by Michael N. Helmus (a co-inventor of the present invention) entitled "Medical Device Design—A Systems Approach: Central Venous Catheters", 22nd International Society for the Advancement of Material and Process Engineering Technical Conference (1990) relates to polymer/drug/membrane systems for releasing heparin. Those polymer/drug/membrane systems require two distinct types of layers to function.

It has been recognized that contacting blood with the surface of a foreign body in vivo has a tendency to induce thrombogenic responses and that as the surface area of a foreign device in contact with host blood increases, the tendency for coagulation and clot forming at these surfaces also increases. This has led to the use of immobilized systemic anti-coagulant or thrombolytic agents such as heparin on blood contacting surfaces such as oxygen uptake devices to reduce this phenomenon. Such an approach is described by Winters, et al., in U.S. Pat. Nos. 5,182,317; 5,262,451 and 5,338,770 in which the amine functional groups of the active material are covalently bonded using polyethylene oxide (PEO) on a siloxane surface.

Another approach is described in U.S. Pat. No. 4,613,665 to Larm in which heparin is chemically covalently bound to plastic surface materials containing primary amino groups to impart a non-thrombogenic surface to the material. Other approaches for bonding heparin are described in Barbucci, et al., "Coating of commercially available materials with a new heparinizable material", *Journal of Biomedical Materials Research*, Vol 25, 1259–1274 (1991); Hubbell, J. A., "Pharmacologic Modification of Materials", *Cardiovascular Pathology*, Vol 2, No 3(Suppl.), 121S–127S (1993); Gravlee, G. P., "Heparin-Coated Cardiopulmonary Bypass Circuits", *Journal of Cardiothoracic and Vascular Anesthesia*, Vol 8, No 2, pp 213–222 (1994).

Although polymeric stents are effective, they, may have mechanical properties that are inferior to those of metal stents of like thickness and weave. Metallic vascular stents braided of even relatively fine metal can provide a large amount of strength to resist inwardly directed circumferential pressure. A polymer material of comparable strength requires a much thicker-walled structure or heavier, denser filament weave, which in turn, reduces the cross-sectional area available for flow through the stent and/or reduces the relative amount of open space in the weave. Also, it is usually more difficult to load and deliver polymeric stents using catheter delivery systems.

While certain types of stents such as braided metal stents may be preferred for some applications, the coating and coating modification process of the present invention is not so limited and can be used on a wide variety of prosthetic devices. Thus, in the case of stents, the present invention also applies, for example, to the class of stents that are not self-expanding including those which can be expanded, for instance, with a balloon; and is applicable to polymeric stents of all kinds. Other medical devices that can benefit from the present invention include blood exchanging devices, vascular access ports, central venus catheters, cardiovascular catheters, extracorpeal circuits, vascular grafts, pumps, heart valves, and cardiovascular sutures, to name a few. Regardless of detailed embodiments, applicability of the invention should not be considered limited with respect to implant design, implant location or materials of construction. Further, the present invention may be used with other types of implantable prostheses.

Accordingly, it is a primary object of the present invention to provide a coating and process for coating a stent to be used as a deployed stent prostheses, the coating being capable of effective controlled long-term delivery of biologically active materials.

Another object of the invention is to provide a coating and process for coating a stent prostheses using a biostable hydrophobic elastomer in which biologically active species are incorporated within a coating.

Still another object of the present invention is to provide a multi-layer coating and process for the delivery of biologically active species in which the percentage of active material can vary from layer to layer.

Yet another object of the present invention is to provide a multi-layer coating and process for the delivery of biologically active species from a coating with a non-thrombogenic surface.

A further object of the invention is to provide a multi-layer coating for the delivery of biologically active species such as heparin having a fluorosilicone top layer.

A still further object of the invention is to provide a multi-layer coating for the delivery of biologically active species such as heparin having a surface containing immobilized polyethylene glycol (PEG).

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

SUMMARY OF THE INVENTION

The present invention provides a relatively thin layered coating of biostable elastomeric material containing an amount of biologically active material dispersed therein in combination with a non-thrombogenic surface that is useful for coating the surfaces of prostheses such as deployable stents.

The preferred stent to be coated is a self-expanding, open-ended tubular stent prostheses. Although other materials, including polymer materials, can be used, in the preferred embodiment, the tubular body is formed of a self-expanding open braid of fine single or polyfilament metal wire which flexes without collapsing, readily axially deforms to an elongate shape for transluminal insertion via a vascular catheter and resiliently expands toward predetermined stable dimensions upon removal in situ.

In the process, the initial coating is preferably applied as a mixture, solution or suspension of polymeric material and finely divided biologically active species dispersed in an organic vehicle or a solution or partial solution of such species in a solvent or vehicle for the polymer and/or biologically active species. For the purpose of this application, the term "finely divided" means any type or size of included material from dissolved molecules through suspensions, colloids and particulate mixtures. The active material is dispersed in a carrier material which may be the polymer, a solvent, or both. The coating is preferably applied as a plurality of relatively thin layers sequentially applied in relatively rapid sequence and is preferably applied with the stent in a radially expanded state.

In many applications the layered coating is referred to or characterized as including an undercoat and topcoat. The coating thickness ratio of the topcoat to undercoat may vary with the desired effect and/or the elution system. Typically these are of different formulations with most or all of the active material being contained in the undercoat and a non-thrombogenic surface is found in the topcoat.

The coating may be applied by dipping or spraying using evaporative solvent materials of relatively high vapor pressure to produce the desired viscosity and quickly establish coating layer thicknesses. The preferred process is predicated on reciprocally spray coating a rotating radially expanded stent employing an air brush device. The coating process enables the material to adherently conform to and cover the entire surface of the filaments of the open structure of the stent but in a manner such that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The coating is exposed to room temperature ventilation for a predetermined time (possibly one hour or more) for solvent vehicle evaporation. In the case of certain undercoat materials, thereafter the polymer material is cured at room temperature or elevated temperatures. Curing is defined as the process of converting the elastomeric or polymeric material into the finished or useful state by the application of heat and/or chemical agents which induce physico-chemical changes. Where, for example, polyurethane thermoplastic elastomers are used as an undercoat material, solvent evaporation can occur at room temperature rendering the undercoat useful for controlled drug release without further curing.

The applicable ventilation time and temperature for cure are determined by the particular polymer involved and particular drugs used. For example, silicone or polysiloxane materials (such as polydimethylsiloxane) have been used successfully. Urethane pre-polymers can also be utilized. Unlike the polyurethane thermoplastic elastomers, some of these materials are applied as pre-polymers in the coating composition and must thereafter be heat cured. The preferred silicone species have relatively low cure temperatures and are known as a room temperature vulcanizable (RTV) materials. Some polydimethylsiloxane materials can be cured, for example, by exposure to air at about 90° C. for a period of time such as 16 hours. A curing step may be implemented both after application of the undercoat or a certain number of lower layers and the top layers or a single curing step used after coating is completed.

The coated stents may thereafter be subjected to a post-cure process which includes an inert gas plasma treatment, and sterilization which may include gamma radiation, ETO treatment, electron beam or steam treatment.

In the plasma treatment, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20–50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to

the reaction chamber for the plasma treatment. One method uses argon (Ar) gas, operating at a power range from 200 to 400 watts, a flow rate of 150–650 standard ml per minute, which is equivalent to about 100–450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

In accordance with the invention, the top coat or surface coating may be applied in any of several ways to further control thrombolitic effects and optionally, control the release profile especially the initial very high release rate associated with the elution of heparin.

In one embodiment, an outer layer of fluorosilicone (FSi) is applied to the undercoat as a topcoat. The outer layer can also contain heparin. In another embodiment, polyethylene glycol (PEG) is immobilized on the surface of the coating. In this process, the underlayer is subjected to inert gas plasma treatment and immediately thereafter is treated by ammonia (NH_3) plasma to aminate the surface. Amination, as used in this application, means creating mostly imino groups and other nitro containing species on the surface. This is followed by immediate immersion into electrophillically activated polyethylene glycol(PEG) solution with a reductive agent, i.e., sodium cyanoborohydride.

The coated and cured stents having the modified outer layer or surface are subjected to a final gamma radiation sterilization nominally at 2.5–3.5 Mrad. Argon (Ar) plasma treated stents enjoy full resiliency after radiation whether exposed in a constrained or non-constrained status, while constrained stents subjected to gamma sterilization without Ar plasma pretreatment lose resiliency and do not recover at a sufficient or appropriate rate.

The elastomeric materials that form the stent coating underlayers should possess certain properties. Preferably the layers should be of suitable hydrophobic biostable elastomeric materials which do not degrade. Surface layer material should minimize tissue rejection and tissue inflammation and permit encapsulation by tissue adjacent the stent implantation site. Exposed material is designed to reduce clotting tendencies in blood contacted and the surface is preferably modified accordingly. Thus, underlayers of the above materials are preferably provided with a fluorosilicone outer coating layer which may or may not contain imbedded bioactive material, such as heparin. Alternatively, the outer coating may consist essentially of polyethylene glycol (PEG), polysaccharides, phospholipids, or combinations of the foregoing.

Polymers generally suitable for the undercoats or underlayers include silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, polyamide elastomers, and EPDM rubbers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention. Surface layer materials include fluorosilicones and polyethylene glycol (PEG), polysaccharides, phospholipids, and combinations of the foregoing.

While heparin is preferred as the incorporated active material, agents possibly suitable for incorporation include antithrobotics, anticoagulants, antibiotics, antiplatelet agents, thorombolytics, antiproliferatives, steroidal and non-steroidal antinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive action may come from inhibiting particular cells (e.g., smooth muscle cells) or tissue formation (e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

Suitable materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemoried alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Further details concerning the fabrication and details of other aspects of the stents themselves may be gleaned from the above referenced U.S. Pat. Nos. 4,655,771 and 4,954,126 to Wallsten and U.S. Pat. No. 5,061,275 to Wallsten et al, which are incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

For the purposes of this specification, "elution" is defined as any process of release that involves extraction or release by direct contact of the material with bodily fluids through the interparticle paths connected with the exterior of the coating. "Transport" or "diffusion" are defined to include a mechanism of release in which the material released traverses through another material.

The desired release rate profile can be tailored by varying the coating thickness, the radial distribution (layer to layer) of bioactive materials, the mixing method, the amount of bioactive material, the combination of different matrix polymer materials at different layers, and the crosslink density of the polymeric material. The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, during the curing process, determines the amount of crosslinking and also the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as heparin, a denser crosslink structure will result in a longer release time and reduced burst effect.

It will also be appreciated that an unmedicated silicone thin top layer provides some advantage and additional control over drug elusion; however, in the case of heparin, for example, it has been found that a top coat or surface coating modified to further control the initial heparin release profile or to make the surface more non-thrombogenic presents a distinct advantage.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate like parts throughout the same:

FIG. **1** is a schematic flow diagram illustrating the steps of the process of the invention;

FIG. **2** represents a release profile for a multi-layer system showing the percentage of heparin released over a two-week period;

FIG. **3** represents a release profile for a multi-layer system showing the relative release rate of heparin over a two-week period;

FIG. **4** illustrates a profile of release kinetics for different drug loadings at similar coating thicknesses illustrating the release of heparin over a two-week period without associated means to provide a long term non-thrombogenic surface thereafter;

FIG. **5** illustrates drug elution kinetics at a given loading of heparin over a two-week period at different coating thicknesses without associated means to provide a long term non-thrombogenic surface thereafter;

FIG. **6** illustrates the release kinetics for a given undercoat and topcoat material varied according to thickness in which the percentage heparin in the undercoat and topcoats are kept constant;

FIG. **7** is a plot of heparin release kinetics in phosphate buffer system at PH 7.4 with and without fluorosilicone (FSi) topcoat; and

FIG. **8** is another plot of heparin release kinetics in phosphate buffer system in which a topcoat containing fluorosilicone (FSi) only is compared with an FSi topcoat containing 16.7% imbedded heparin.

DETAILED DESCRIPTION

According to the present invention, the stent coatings incorporating biologically active materials for timed delivery in situ in a body lumen of interest are preferably sprayed in many thin layers from prepared coating solutions or suspensions. The steps of the process are illustrated generally in FIG. **1**. The coating solutions or suspensions are prepared at **10** as will be described later. The desired amount of crosslinking agent (if any) is added to the suspension/solution as at **12** and material is then agitated or stirred to produce a homogenous coating composition at **14** which is thereafter transferred to an application container or device which may be a container for spray painting at **16**. Typical exemplary preparations of coating solutions that were used for heparin and dexamethasone appear next.

General Preparation of Heparin Undercoating Composition

Silicone was obtained as a polymer precursor in solvent (xylene) mixture. For example, a 35% solid silicone weight content in xylene was procured from Applied Silicone, Part #40,000. First, the silicone-xylene mixture was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated amounts of finely divided heparin (2–6 microns) were added into the silicone, then tetrahydrofuron (THF) HPCL grade (Aldrich or EM) was added. For a 37.5% heparin coating, for example: $W_{silicone}$=5 g; solid percent=35%; W_{hep}=5×0.35×0.375/(0.625)=1.05 g. The amount of THF needed (44 ml) in the coating solution was calculated by using the equation $W_{silicone\ solid}/V_{THF}$=0.04 for a 37.5% heparin coating solution). Finally, the manufacturer crosslinker solution was added by using Pasteur P-pipet. The amount of crosslinker added was formed to effect the release rate profile. Typically, five drops of crosslinker solution were added for each five grams of silicone-xylene mixture. The solution was stirred by using the stirring rod until the suspension was homogenous and milk-like. The coating solution was then transferred into a paint jar in condition for application by air brush.

General Preparation of Dexamethasone Undercoating Composition

Silicone (35% solution as above) was weighed into a beaker on a Metler balance. The weight of dexamethasone free alcohol or acetate form was calculated by silicone weight multiplied by 0.35 and the desired percentage of dexamethasone (1 to 40%) and the required amount was then weighed. Example: $W_{silicone}$=5 g; for a 10% dexamethasone coating, W_{dex}=5×0.35×0.1/0.9=0.194 g and THF needed in the coating solution calculated. $W_{silicone\ solid}/V_{THF}$=0.06 for a 10% dexamethasone coating solution. Example: $W_{silicone}$=5 g; V_{THF}=5×0.35/0.06≈29 ml. The dexamethasone was weighed in a beaker on an analytical balance and half the total amount of THF was added. The solution was stirred well to ensure full dissolution of the dexamethasone. The stirred DEX-THF solution was then transferred to the silicone container. The beaker was washed with the remaining THF and this was transferred to the silicone container. The crosslinker was added by using a Pasteur pipet. Typically, five drops of crosslinker were used for five grams of silicone.

The application of the coating material to the stent was quite similar for all of the materials and the same for the heparin and dexamethasone suspensions prepared as in the above Examples. The suspension to be applied was transferred to an application device, at **16** in FIG. **1**. Typically a paint jar attached to an air brush, such as a Badger Model 150, supplied with a source of pressurized air through a regulator (Norgren, 0–160 psi) was used. Once the brush hose was attached to the source of compressed air downstream of the regulator, the air was applied. The pressure was adjusted to approximately 15–25 psi and the nozzle condition checked by depressing the trigger.

Any appropriate method can be used to secure the stent for spraying and rotating fixtures were utilized successfully in the laboratory. Both ends of the relaxed stent were fastened to the fixture by two resilient retainers, commonly alligator clips, with the distance between the clips adjusted so that the stent remained in a relaxed, unstretched condition. The rotor was then energized and the spin speed adjusted to the desired coating speed, nominally about 40 rpm.

With the stent rotating in a substantially horizontal plane, the spray nozzle was adjusted so that the distance from the nozzle to the stent was about 2–4 inches and the composition was sprayed substantially horizontally with the brush being directed along the stent from the distal end of the stent to the proximal end and then from the proximal end to the distal end in a sweeping motion at a speed such that one spray cycle occurred in about three stent rotations. Typically a pause of less than one minute, normally about one-half minute, elapsed between layers. Of course, the number of coating layers did and will vary with the particular application. For example, typical tie-layers as at **18** in FIG. **1**, for a coating level of 3–4 mg of heparin per cm^2 of projected area, 20 cycles of coating application are required and about 30 ml of solution will be consumed for a 3.5 mm diameter by 14.5 cm long stent.

The rotation speed of the motor, of course, can be adjusted as can the viscosity of the composition and the flow rate of the spray nozzle as desired to modify the layered structure. Generally, with the above mixes, the best results have been obtained at rotational speeds in the range of 30–50 rpm and with a spray nozzle flow rate in the range of 4–10 ml of coating composition per minute, depending on the stent size. It is contemplated that a more sophisticated, computer-controlled coating apparatus will successfully automate the process demonstrated as feasible in the laboratory.

Several applied layers make up what is called the undercoat as at **18**. In one process, additional upper undercoat

layers, which may be of the same or different composition with respect to bioactive material, the matrix polymeric materials and crosslinking agent, for example, may be applied as the top layer as at **20**. The application of the top layer follows the same coating procedure as the undercoat with the number and thickness of layers being optional. Of course, the thickness of any layer can be adjusted by adjusting the speed of rotation of the stent and the spraying conditions. Generally, the total coating thickness is controlled by the number of spraying cycles or thin coats which make up the total coat.

As shown at **22** in FIG. **1**, the coated stent is thereafter subjected to a curing step in which the pre-polymer and crosslinking agents cooperate to produce a cured polymer matrix containing the biologically active species. The curing process involves evaporation of the solvent xylene, THF, etc. and the curing and crosslinking of the polymer. Certain silicone materials can be cured at relatively low temperatures, (i.e. RT-50° C.) in what is known as a room temperature vulcanization (RTV) process. More typically, however, the curing process involves higher temperature curing materials and the coated stents are put into an oven at approximately 90° C. or higher for approximately 16 hours. The temperature may be raised to as high as 150° C. for dexemethasane containing coated stents. Of course, the time and temperature may vary with particular silicones, crosslinkers and biologically active species.

Stents coated and cured in the manner described need to be sterilized prior to packaging for future implantation. For sterilization, gamma radiation is a preferred method particularly for heparin containing coatings; however, it has been found that stents coated and cured according to the process of the invention subjected to gamma sterilization may be too slow to recover their original posture when delivered to a vascular or other lumen site using a catheter unless a pretreatment step as at **24** is first applied to the coated, cured stent.

The pretreatment step involves an argon plasma treatment of the coated, cured stents in the unconstrained configuration. In accordance with this procedure, the stents are placed in a chamber of a plasma surface treatment system such as a Plasma Science 350 (Himont/Plasma Science, Foster City, Calif.). The system is equipped with a reactor chamber and RF solid-state generator operating at 13.56 mHz and from 0–500 watts power output and being equipped with a microprocessor controlled system and a complete vacuum pump package. The reaction chamber contains an unimpeded work volume of 16.75 inches (42.55 cm) by 13.5 inches (34.3 cm) by 17.5 inches (44.45 cm) in depth.

In the plasma process, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20–50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150–650 standard ml per minute, which is equivalent to 100–450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After this, as shown at **26**, the stents may be exposed to gamma sterilization at 2.5–3.5 Mrad. The radiation may be carried out with the stent in either the radially non-constrained status—or in the radially constrained status.

Preferably, however, the surface is modified prior to plasma treatment or just prior to sterilization by one of several additional processing methods of which some are described in relation to the following examples.

EXAMPLE 1

Fluorosilicone Surface Treatment of Eluting Heparin Coating

The undercoat of a stent was coated as multiple applied layers as described above thereafter and cured as described at **22**. The heparin content of the undercoat was 37.5% and the coating thickness was about 30–40μ. Fluorosilicone (FSi) spray solution was prepared at **30** from a fluorosilicone suspension (Applied Silicone #40032) by weighing an amount of fluorosilicone suspension and adding tetrahydrofuran (THF) according to the relation equation of V_{THF}= 1.2×the weight of fluorosilicone suspension. The solution was stirred very well and spray-coated on the stent at **32** using the technique of the application of the undercoat process at **18** and the coated stents were cured at 90° C. for 16 hours. The coated stents are argon plasma treated prior to gamma sterilization according to the procedures described above in accordance with steps 22–26.

FIG. **7** is a plot of heparin release kinetics in phosphate buffer system with fluorosilicone topcoat and without any topcoat. The thickness of the topcoat is about 10–15μ. While it does not appear on the graph of FIG. **7**, it should be noted that the release rate for the coating without FSi is initially about 25 times higher than that with FSi, i.e., during the first 2 hours. This is, of course, clearly off the scale of the graph. It is noteworthy, however, that the coating with the FSi top layer or diffusion barrier does show a depressed initial release rate combined with an enhanced elusion rate after the first day and through the first week up until about the tenth day. In addition, the fluorosilicone (FSi) topcoat, by virtue of the high electro-negativity of fluorination maintains non-thrombogenic surface qualities during and after the elusion of the biologically active heparin species. In addition, because of the negative charges on the heparin itself, the electro-negativity of the fluorosilicone topcoat may be, at least in part, responsible for the modified heparin release kinetic profile.

FIG. **8** compares a plot of fluorosilicone (FSi) top coating containing 16.7% imbedded heparin with one containing fluorosilicone (FSi) only. An undercoating is identical to that utilized in FIG. **7** containing about 37.5% heparin to a thickness of about 30–40 microns. These elution kinetics are quite comparable with the heparin-free FSi top layer greatly reducing the initial burst of heparin release and otherwise the heparin in the FSi top layer imparts a slightly greater release over the period of the test.

EXAMPLE 2

Immobilization of Polyethylene Glycol (PEG) on Drug Eluting Undercoat

An undercoat was coated on a stent and cured at **22** as in Example 1. The stent was then treated by argon gas plasma as at **24** and ammonium gas plasma at **40**. The equipment and the process of argon gas plasma treatment was as has been described above. The ammonium plasma treatment was implemented immediately after the argon gas plasma treatment, to aminate the surface of the coating. The ammonium flow rate was in the range of 100–700 cubic centimeter per minute (ccM) in preferably in the range of 500–600 ccM. The power output of radio frequency plasma was in the range of 50–500 watts, preferably in ~200 watts. The process time was in the range of 30 sec–10 min, preferably ~5 min.

Immediately after amination, the stents were immersed into electrophilically activated polyethylene glycol (PEG)

solution at **42**. PEG is known to be an inhibitor of protein absorption. Examples of electrophilically activated PEG are PEG nitrophenyl carbonates, PEG trichlorophenyl carbonates, PEG tresylate, PEG glycidyl ether, PEG isocyanate, etc., optionally with one end terminated with methoxyl group. Molecular weight of PEG ranged from about 1000–6000, and is preferable about 3000. It has been observed that simple ammonium amination will not generate large quantities of primary and secondary amines on the elastomeric polymer surface (for example silicone). Instead, imine (>C═N—H), and other more oxidative nitro containing groups will dominate the surface. It is generally necessary to add reductive agent such as $NaBH_3CN$ into the reaction media so that the functional group on PEG can react with imine and possibly other nitro-containing species on the surface, and therefore immobilize PEG onto the surface. The typical concentration of $NaBH_3CN$ is about 2 mg/ml. Since PEG and its derivatives dissolve in water and many polar and aromatic solvents, the solvent used in the coating must be a solvent for PEG but not for the drug in the undercoat to prevent the possible loss of the drug through leaching. In the case of eluting-heparin coating, a mixed solvent of formamide and methyl ethyl ketone (MEK) or a mixed solvent of formamide and acetone are preferred solvents (preferably at ratios of 30 formamide: 70 MEK or acetone by volume), since they will not dissolve heparin. The concentration of PEG, the reaction time, the reaction temperature and the pH value depend on the kind of PEG employed. In the case of eluting heparin coating, 5% PEG tresylate in (30–70) Formamide/MEK was used successfully. The reaction time was 3 hours at room temperature. PEG was then covalently bound to the surface. Gamma radiation was then used for sterilization of this embodiment as previously described.

With respect to the anticoagulant material heparin, the percentage in the undercoat is nominally from about 30–50% and that of the topcoat from about 0–30% active material. The coating thickness ratio of the topcoat to the undercoat varies from about 1:10 to 1:2 and is preferably in the range of from about 1:6 to 1:3.

Suppressing the burst effect also enables a reduction in the drug loading or in other words, allows a reduction in the coating thickness, since the physician will give a bolus injection of antiplatelet/anticoagulation drugs to the patient during the stenting process. As a result, the drug imbedded in the stent can be fully used without waste. Tailoring the first day release, but maximizing second day and third day release at the thinnest possible coating configuration will reduce the acute or subacute thrombosis.

FIG. **4** depicts the general effect of drug loading for coatings of similar thickness. The initial elution rate increases with the drug loading as shown in FIG. **5**. The release rate also increases with the thickness of the coating at the same loading but tends to be inversely proportional to the thickness of the topcoat as shown by the same drug loading and similar undercoat thickness in FIG. **6**.

What is apparent from the data gathered to date, however, is that the process of the present invention enables the drug elution kinetics to be controlled in a manner desired to meet the needs of the particular stent application. In a similar manner, stent coatings can be prepared using a combination of two or more drugs and the drug release sequence and rate controlled. For example, antiproliferation drugs may be combined in the undercoat and antiplatelet drugs in the topcoat. In this manner, the antiplatelet drugs, for example, heparin, will elute first followed by antiproliferation drugs to better enable safe encapsulation of the implanted stent.

The heparin concentration measurement were made utilizing a standard curve prepared by complexing azure A dye with dilute solutions of heparin. Sixteen standards were used to compile the standard curve in a well-known manner.

For the elution test, the stents were immersed in a phosphate buffer solution at pH 7.4 in an incubator at approximately 37° C. Periodic samplings of the solution were processed to determine the amount of heparin eluted. After each sampling, each stent was placed in heparin-free buffer solution.

As stated above, while the allowable loading of the elastomeric material with heparin may vary, in the case of silicone materials heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In the case of dexamethasone, the loading may be as high as 50% or more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a thin surface coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

Whereas the above examples depict coatings having two different drug loadings or percentages of biologically active material to be released, this is by no means limiting with respect to the invention and it is contemplated that any number of layers and combinations of loadings can be employed to achieve a desired release profile. For example, gradual grading and change in the loading of the layers can be utilized in which, for example, higher loadings are used in the inner layers. Also layers can be used which have no drug loadings at all. For example, a pulsatile heparin release system may be achieved by a coating in which alternate layers containing heparin are sandwiched between unloaded layers of silicone or other materials for a portion of the coating. In other words, the invention allows untold numbers of combinations which result in a great deal of flexibility with respect to controlling the release of biologically active materials with regard to an implanted stent. Each applied layer is typically from approximately 0.5 microns to 15 microns in thickness. The total number of sprayed layers, of course, can vary widely, from less than 10 to more than 50 layers; commonly, 20 to 40 layers are included. The total thickness of the coating can also vary widely, but can generally be from about 10 to 200 microns.

Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials

include silicone rubber elastomers and biostable polyurethanes specifically.

This invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use embodiments of the example as required. However, it is to be understood that the invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

We claim:

1. A medical device having at least a portion which is implantable into the body of a patient, wherein at least a part of the device portion is metallic and at least part of the metallic device portion is covered with a coating for release of at least one biologically active material, wherein said coating comprises an undercoat comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed release therefrom, and wherein said coating further comprises a topcoat which at least partially covers the undercoat, said topcoat comprising a biostable, non-thrombogenic material which provides long term non-thromobogenicity to the device portion during and after release of the biologically active material, and wherein said topcoat is substantially free of an elutable material.

2. The device of claim **1** wherein said biologically active material is heparin.

3. The device of claim **2** wherein the non-thrombogenic material is selected from the group consisting of fluorosilicone, polyethylene glycol (PEG), polysaccharides, phospholipids and combinations thereof.

4. The device of claim **3** wherein the non-thrombogenic material is fluorosilicone.

5. The device of claim **3** wherein the non-thrombogenic material is polyethylene glycol (PEG).

6. The device of claim **1** wherein the medical device is an expandable stent.

7. The device of claim **1** wherein the topcoat consists of a polymer.

8. The device of claim **6** wherein the stent comprises a tubular body having open ends and an open lattice sidewall structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

9. A stent for implantation in a vascular lumen comprising a tubular body having open ends and a sidewall and a coating on at least a part of a surface of said sidewall, said coating further comprising an undercoat comprising a hydrophobic elastomeric material incorporating an amount of finely divided heparin therein for timed release therefrom, and wherein said coating further comprises a topcoat comprising an amount of fluorosilicone which is capable of providing long term non-thrombogenicity to the surface during and after release of the biologically active material, wherein said topcoat at least partially covers the undercoat, and wherein said topcoat is substantially free of an elutable material.

10. The device of claim **9** wherein the sidewall is an open lattice structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

11. A stent for implantation in a vascular lumen comprising a tubular body having open ends and a sidewall and a coating on at least a part of the surface of said sidewall, said coating further comprising an undercoat comprising a hydrophobic elastomeric material incorporating an amount of finely divided heparin therein for timed release therefrom, and wherein said coating further comprises a topcoat comprising an amount of polyethylene glycol (PEG) which is capable of providing long term non-thrombogenicity to the surface during and after release of the biologically active material, wherein said topcoat at least partially covers the undercoat, and wherein said topcoat is substantially free of an elutable material.

12. The device of claim **11** wherein the sidewall is an open lattice structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

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US007217286B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 7,217,286 B2**
(45) **Date of Patent: *May 15, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

(75) Inventors: **Robert Falotico**, Bell Mead, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

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This patent is subject to a terminal disclaimer.

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(51) **Int. Cl.**
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(52) **U.S. Cl.** **623/1.42**

(58) **Field of Classification Search** 623/1.45–1.48; 427/2.1–2.31
See application file for complete search history.

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Primary Examiner—Suzette Gherbi
(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

5 Claims, 2 Drawing Sheets

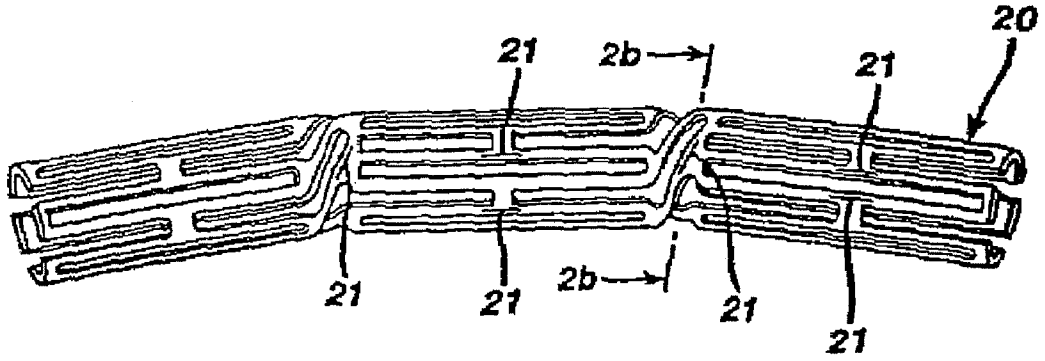

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FIG. 1

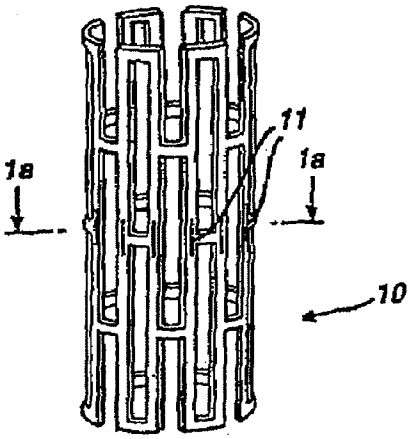


FIG. 1a

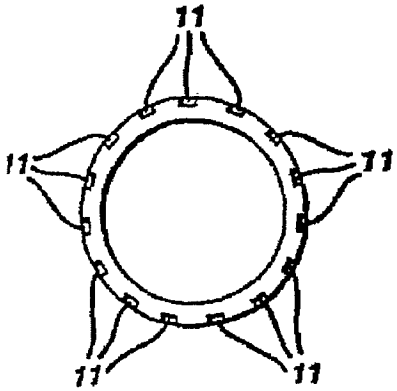


FIG. 2a

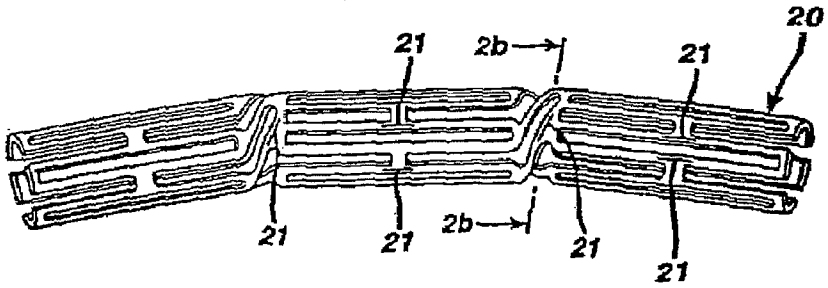


FIG. 2b

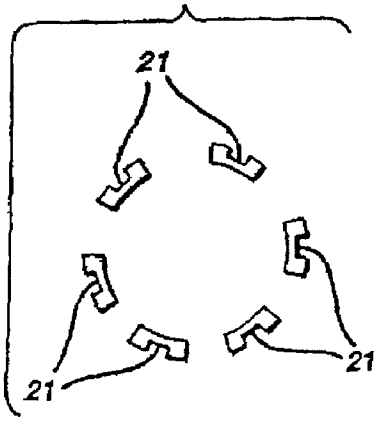


FIG. 3a

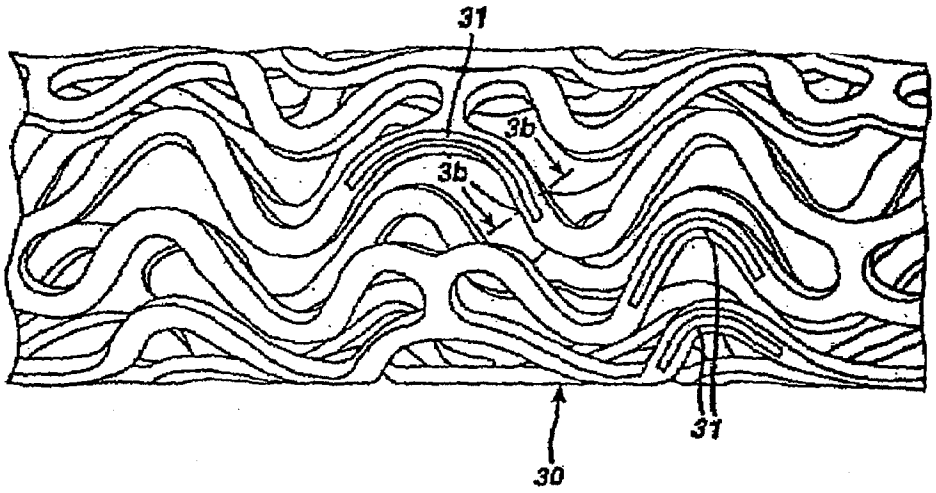


FIG. 3b

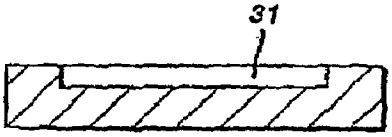
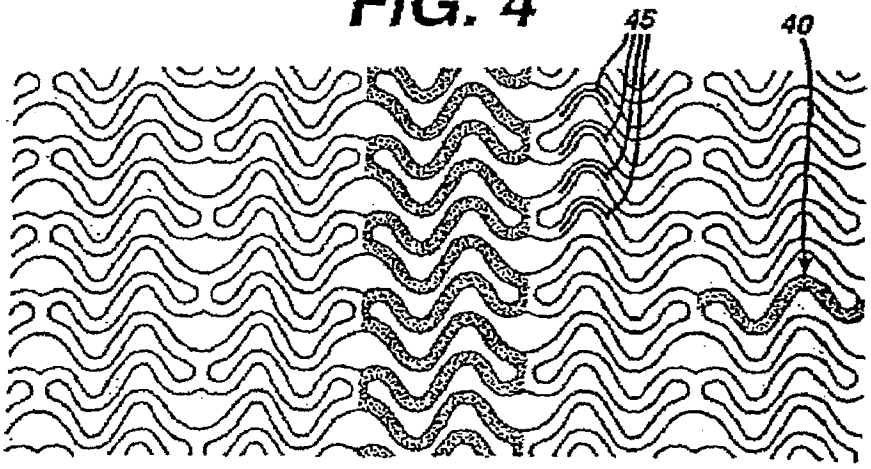


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/951,385, filed Sep. 28, 2004, now pending, which in turn is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which in turn is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997. The disclosures of these prior applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transiuminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a *contractile* phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF),

etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotype to a synthetic phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: Vascular Smooth Muscle Cells in Culture, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca.Ratioh, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which FIGS. **1** and **1A** are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 Circulation, 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 2-32-242 (1993); Serruys, P. W. et al., 88 Circulation, (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction

in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25–626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611–616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986);. Majesky et al., 61 Circ Res., 296–300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 Neurosurgery, 92–898, (1989) colchicine (Currier, J. W. et al., 80 Circulation, 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppi. B); 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 Science, 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167–11747 (1989), trapidil (Liu, M. W. et al., 81 Circulation, 1089–1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 J. Circulation, 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B-117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G.sub.1 to 5 phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods: These can vary:

- Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.
- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.
- or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.
- or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.
- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake.
- Extravascular delivery by the pericardial route.
- Extravascular delivery by the advential application of sustained release formulations.

Uses:

- for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.
- prevention of tumor expansion from stents.
- preventingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the

stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether:

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery:

A: Polymeric Sheet

Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolid-e) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10.mu. to 1000.mu. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating:

Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed:

1. A device comprising a metallic stent, a biocompatible, nonabsorbable polymeric carrier, and a therapeutic agent, wherein:

said polymeric carrier comprises an acrylate-based polymer or copolymer, a fluorinated polymer, or a mixture thereof, and

said therapeutic agent is rapamycin, or a macrocyclic lactone analog thereof, and is present in an amount effective to inhibit neointimal proliferation.

2. The device according to claim **1** wherein said therapeutic agent is a macrocyclic lactone analog of rapamycin.

3. The device according to claim **1** that provides a controlled release of said therapeutic agent over a period of several weeks.

4. The device according to claim **2** that provides a controlled release of said therapeutic agent over a period of several weeks.

5. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a device according to any one of claims **1** to **4** in the lumen of said coronary artery.

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